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March 16, 2021

VIA ECF
The Honorable Freda L. Wolfson, Chief, U.S.D.J.
United States District Court for the District of New Jersey
Clarkson S. Fisher Building & U.S. Courthouse
402 East State Street
Trenton, NJ 08608

Re: In Re: Fosamax Products Liability Litigation
Civil Action No. 08-08 (FLW)(LHG)

Dear Judge Wolfson,

This firm represents defendant Merck Sharp & Dohme Corp. ("Merck") in the above referenced matter. I write to inform the Court of a new decision that bears on the parties' pending submissions regarding preemption: *In re Incretin-Based Therapies Prods. Liab. Litig.*, No. 13-md-2452, 2021 WL 880316 (S.D. Cal. Mar. 9, 2021) (slip op. attached as Exh. A). That decision held that failure-to-warn claims against Merck and other manufacturers were preempted in light of "clear evidence that the FDA would not approve" the plaintiffs' requested label. (Exh. A at 26.) In doing so, the court agreed with Merck's position here that the "clear evidence" inquiry takes into account all FDA action within the scope of its congressionally delegated authority, and can be further informed by FDA "inaction" in light of its statutory and regulatory obligations. (*Id.* at 28, 31.) Merck addressed these issues on pages 20-23 and 28-30 of its opening brief (Dkt. 4483) and pages 11-12 and 14-15 of its reply brief (Dkt. 4484).

Respectfully submitted,

/s/ Karen A. Confoy

Karen A. Confoy

KAC:nmn
Enclosure

EXHIBIT A

2021 WL 880316
Only the Westlaw citation is currently available.
United States District Court, S.D. California.

IN RE INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION
As to All Related and Member Cases

Case No.: 13-md-2452-AJB-MDD
|
Signed 03/09/2021

OMNIBUS ORDER:

(1) GRANTING DEFENDANTS' JOINT MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION;

(2) GRANTING DEFENDANTS' JOINT MOTION TO EXCLUDE DRS. MADIGAN, WELLS, BROWN, AND GALE;

(3) GRANTING DEFENDANTS' JOINT MOTION TO EXCLUDE DRS. LANDOLPH, WOOLF, AND TAYLOR;

(4) DENYING AS MOOT PLAINTIFFS' MOTION TO EXCLUDE DRS. THAYER, WANG, AND SCHARFSTEIN;

(5) GRANTING DEFENDANT MERCK'S MOTION FOR SUMMARY JUDGMENT BASED ON CAUSATION;

(6) GRANTING DEFENDANTS AMYLIN AND LILLY'S MOTION FOR SUMMARY JUDGMENT BASED ON CAUSATION; and

(7) GRANTING DEFENDANT NOVO'S MOTION FOR SUMMARY JUDGMENT BASED ON CAUSATION.

Anthony J. Battaglia, United States District Judge

I. INTRODUCTION

***1** Pancreatic cancer is an unrelenting disease, occurring at a rate of more than 50,000 cases a year. It is a leading cause of cancer-related death in the United States and has caused, and continues to cause, much suffering to tens of thousands of Americans each year. This multidistrict litigation involves claims that Defendants failed to warn that four prescription brand-name drugs used to treat type 2 diabetes cause, or increase the risk of, pancreatic cancer. Plaintiffs are individuals diagnosed with type 2 diabetes who were prescribed and consumed one or more of the following prescription drugs: Byetta, Januvia, Janumet, and Victoza. Defendants are the pharmaceutical companies that manufacture and market the drugs: Amylin Pharmaceuticals, LLC ("Amylin"), Eli Lilly and Company ("Lilly"), Merck Sharp & Dohme Corp. ("Merck"), and Novo Nordisk Inc. ("Novo") (collectively, "Defendants").

The drugs are sometimes referred to by their active ingredients. [1] Exenatide is the active ingredient in Amylin and Lilly's Byetta. Sitagliptin is the active ingredient in Merck's Januvia and Janumet. Liraglutide is the active ingredient in Novo's Victoza. The therapies involve incretin hormones, which operate in the body to lower blood sugar by stimulating or sustaining production of insulin. Exenatide and liraglutide are glucagon-like peptide-1 ("GLP-1") receptor agonists ("GLP-1 RAs"). Sitagliptin is a dipeptidyl peptidase-4 ("DPP-4") inhibitor ("DPP-4i"). Although the therapies are different classes of drugs, the FDA has generally reviewed and recognized them under the broader terms of incretin mimetics or incretin-based therapies. Up until now, the parties did too, focusing their arguments on incretin-based drugs collectively. Now, their arguments also discuss the drugs separately and with respect to their classification as either a GLP-1 RA or DPP-4i.

1 For purposes of this Order, the Court will use the drug's brand name and its active ingredient interchangeably.

Through the enactment of the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. § 301 et seq. ("FDCA"), Congress delegated authority to the Food and Drug Administration ("FDA") to regulate pharmaceutical manufacturers and their products. With subsequent amendments, Congress enlarged this authority, charging the FDA with the power to protect the public health, and to assure the safety, effectiveness, and reliability of drugs. In discharging its regulatory duties, the FDA oversees the introduction of

new drugs into the market, regulates the content of drug labeling, and ensures manufacturers comply with post-marketing requirements. Despite the FDA's broad regulatory duties, a drug manufacturer remains primarily responsible for maintaining the adequacy of product labeling. State tort law is therefore generally viewed as a complimentary form of drug regulation, providing additional protections and recourse for injured consumers. Yet, when state tort law imposes a duty impossible to meet in light of FDA regulations, federal law will preempt state law.

II. BACKGROUND

***2** On November 9, 2015, this Court granted Defendants' motion for summary judgment based on preemption. (Doc. No. 1539.) On appeal, the Ninth Circuit did not reach the preemption question, and instead, remanded the case for the Court to permit certain discovery, consider the materiality of Plaintiffs' asserted new safety information, and reinstate the opinion of Plaintiffs' expert, Dr. Fleming. *In re Incretin-Based Therapies Prod. Liab. Litig.*, 721 F. App'x 580, 581–82, 584 (9th Cir. 2017).

Several years later, and upon completion of supplemental discovery, Defendants renewed their joint motion for summary judgment based on preemption. (Doc. No. 3594.) In addition, Defendants each filed a motion for summary judgment based on lack of general causation as to their respective drugs. [2] (Doc. Nos. 3524, 3525, 3585.) The parties also filed motions to exclude certain experts. (Doc. Nos. 3521, 3586, 3613.) On October 20, 2020, the Court heard oral arguments on the motions and thereafter took the matter under submission. [3]

2 From their briefs, it appears that Amylin and Lilly, who are responsible for Byetta, are jointly defending themselves in the instant motions before this Court. Throughout this Order, the Court will take the parties' lead and refer primarily to Amylin for simplicity.

3 Pursuant to the agreement of all parties and in an effort to promote the convenient and efficient resolution of nearly identical summary judgment and evidentiary motions pending in the state and federal proceedings, the Court held joint oral argument with Judge Highberger of the Los Angeles County Superior Court, who is presiding over the pancreatic cancer cases pending in state court (Case No. JCCP 4272). *See* *In re Phenylpropanolamine (PPA) Products Liab. Litig.*, 460 F.3d 1217, 1222 (9th Cir. 2006) (noting a court's statutory charge in a multidistrict litigation proceeding is to promote the just and efficient conduct of the actions pursuant to 28 U.S.C. § 1407). The Court also participated in a subsequent motion hearing before Judge Highberger on December 8, 2020. While these hearings were held jointly, the Court has deliberated on the case individually and without discussion of the merits with the state court judge.

III. LEGAL STANDARD

Federal Rule of Civil Procedure 56 governs motions for summary judgment. Summary judgment permits a court to enter judgment on factually unsupported claims, *see* *Celotex Corp. v. Catrett*, 477 U.S. 317, 327, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986), and may also be used on affirmative defenses. *Dam v. Gen'l. Elec. Co.*, 265 F.2d 612, 614 (9th Cir. 1958). Granting summary judgment is proper if there is "no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A fact is material when, under the governing substantive law, it could affect the outcome of the case. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). A dispute about a material fact is genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Id.*

The moving party has the initial burden of demonstrating that summary judgment is proper. *See* *Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 152, 90 S.Ct. 1598, 26 L.Ed.2d 142 (1970). The burden then shifts to the opposing party to provide admissible evidence beyond the pleadings to show that summary judgment is not appropriate. *See* *Celotex*, 477 U.S. at 322, 324, 106 S.Ct. 2548. The court must review the record as a whole and draw all reasonable inferences in favor of the non-moving party. *Hernandez v. Spacelabs Med. Inc.*, 343 F.3d 1107, 1112 (9th Cir. 2003). However, unsupported conjecture or conclusory statements are insufficient to defeat summary judgment. *Id.*; *Surrell v. Cal. Water Serv. Co.*, 518 F.3d 1097, 1103 (9th Cir. 2008). "The mere existence of a scintilla of evidence in support of the plaintiff's position will

be insufficient" to survive summary judgment. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). A party opposing summary judgment must come forward with "significant probative evidence tending to support its claim that material, triable issues of fact remain." *Sanchez v. Vild*, 891 F.2d 240, 242 (9th Cir. 1989).

IV. DISCUSSION

***3** Defendants assert that they are entitled to summary judgment because it is impossible to comply with both the FDA's regulatory scheme and state law failure-to-warn requirements, and because there is no genuine dispute of material fact as to general causation. Plaintiffs maintain that Defendants have not established preemption, and that their experts have established a pathway to causation. Both Plaintiffs and Defendants move to exclude certain experts. The Court discusses these motions in turn.

A. PREEMPTION MOTION

The preemption question before the Court is whether Defendants are entitled to summary judgment based on the affirmative defense of federal preemption because it is impossible for Defendants to comply with both the FDA's regulations and the state law failure-to-warn requirements upon which Plaintiffs rest their claims.

1) Relevant Law

Under the Supremacy Clause of the United States Constitution, "Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372, 120 S.Ct. 2288, 147 L.Ed.2d 352 (2000); *see also Oneok, Inc. v. Learjet, Inc.*, 575 U.S. 373, 135 S. Ct. 1591, 1594–95, 191 L.Ed.2d 511 (2015). "This means that when federal and state law conflict, federal law prevails and state law is preempted." *Knox v. Brnovich*, 907 F.3d 1167, 1173 (9th Cir. 2018) (quoting *Murphy v. NCAA*, —— U.S. ——, 138 S. Ct. 1461, 1476, 200 L.Ed.2d 854 (2018)). This case concerns impossibility preemption, which is a type of conflict preemption that occurs when it is "impossible for a private party to comply with both state and federal requirements." *Mutual Pharmaceutical Co. v. Bartlett*, 570 U. S. 472, 480, 133 S.Ct. 2466, 186 L.Ed.2d 607 (2013) (citation omitted).

In the context of pharmaceutical drugs litigation, the Supreme Court held in *Wyeth v. Levine* that a state law claim that a drug manufacturer failed to warn consumers of a risk associated with using its drug is preempted by the FDCA and related labeling regulations, if there is "clear evidence" that the FDA would not have approved a change to the drug's label. 555 U.S. 555, 571, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). Ten years later in *Merck Sharp & Dohme Corp. v. Albrecht*, the Supreme Court clarified that courts should treat the question of whether clear evidence is met "not as a matter of fact for a jury, but as a matter of law for the judge to decide." —— U.S. ——, 139 S. Ct. 1668, 1679, 203 L.Ed.2d 822 (2019). It did "not further define *Wyeth's* use of the 'clear evidence' in terms of evidentiary standards, such as 'preponderance of evidence' or 'clear and convincing evidence.' " *Id.* Instead, a judge must simply answer the question of "whether the relevant federal and state laws 'irreconcilably conflict.' " *Id.* (citation omitted).

To that end, the Supreme Court explained that because the FDA's "changes being effected" ("CBE") regulations permit drug manufacturers to add or strengthen a label without prior approval, 21 C.F.R. § 314.70(c)(6)(iii)(A), "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Id.* at 1679. However, while a manufacturer bears responsibility for maintaining the adequacy of its labels for as long as the drug is on the market, it "cannot propose a change that is not based on reasonable evidence." *Id.* There must be sufficient evidence of a causal association between the drug and the information sought to be added. *Id.* Additionally, the *Albrecht* court held that " 'clear evidence' is evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Id.* at 1672.

2) Whether Federal and State Law "Irreconcilably Conflict"

***4** Turning to whether federal and state laws irreconcilably conflict, Defendants claim that it is impossible to comply with both the FDA's regulatory scheme and state law because (1) Plaintiffs' alleged "newly acquired information" is not material and does not satisfy the requirements of the CBE regulation, and (2) because there is clear evidence that the FDA would have rejected a pancreatic cancer warning in the labels for Byetta, Januvia, Janumet, and Victoza. Plaintiffs contend that Defendants' arguments are incompatible with the Ninth Circuit's order in this case, as well as the Supreme Court's recent decision in *Albrecht*.

As an initial matter, the Court finds that the Ninth Circuit's decision in this case does not foreclose the entry of summary judgment on preemption. Pertinent here, the Ninth Circuit ruled only that the Court should have considered in its earlier preemption analysis whether the FDA reviewed Plaintiffs' new safety information and whether that information would be material to the FDA's conclusion. *In re Incretin-Based Therapies Prod. Liab. Litig.*, 721 F. App'x at 582 (finding that the Court should not have "relied on *Buckman* to deem the plaintiffs' newly discovered evidence 'irrelevant' to the court's preemption analysis at the summary judgment stage"). Nothing in the appellate court's decision prevents the Court from conducting that very analysis here. Indeed, *Albrecht* held that when conducting a preemption analysis, a judge may have to resolve contested brute facts, such as whether a manufacturer submitted all material information to the FDA because such factual questions are part and parcel of the broader legal question and do not warrant submission to a jury. 139 S. Ct. at 1681. Thus, the Court will determine whether the FDA's regulatory scheme and state law failure-to-warn requirements "irreconcilably conflict" and resolve issues regarding materiality along the way. *Id.*

Plaintiffs also contend that *Albrecht* limited preemption to cases where the manufacturer has proposed a label change. (Doc. No. 3721 at 19).[4] The Court, however, does not read *Albrecht* so narrowly. Rather, the Court finds that *Albrecht* simply reiterated the lesson in *Wyeth* that the availability of the CBE label change process makes it such that a manufacturer will not "ordinarily" be able to show an irreconcilable conflict between state and federal law. *Albrecht*, 139 S. Ct. at 1679. Important here, the Supreme Court also recognized that this general principle cannot be applied in every case by expressly stating that "manufacturers cannot propose a change that is not based on reasonable evidence." *Id.* (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). Moreover, the *Albrecht* court noted: "The question of disapproval 'method' is not now before us. And we make only the obvious point that, *whatever the means* the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated." *Id.* (emphasis added).

4 The pinpoint page citations refer to the ECF-generated page numbers at the top of each filing.

Further, the manufacturer in *Albrecht* "conceded that the FDA's CBE regulation would have permitted [it] to try to change the label to add a warning" before the FDA required it do so. 139 S. Ct. at 1675. The manufacturers in this case do not make such a concession. To the contrary, they maintain that the CBE regulations did not permit them to change their labeling because they had no newly acquired information to support the change that Plaintiffs propose. As such, the Court finds *Albrecht* distinguishable in this respect. For these reasons, the Court declines to find that *Albrecht* forecloses preemption merely because there was no CBE or other label change request in this case. *See, e.g., Cerveny v. Aventis, Inc.*, 783 F. App'x 804, 808 n.9 (10th Cir. 2019) (rejecting, post *Albrecht*, the plaintiffs' argument that "only labeling changes sought by the manufacturer can lead to preemption"); *McGrath v. Bayer HealthCare Pharm. Inc.*, 393 F. Supp. 3d 161, 170 (E.D.N.Y. 2019) (similarly distinguishing *Albrecht* based on the manufacturer's concession in that case).

***5** Instead, the Court agrees with Defendants that whether federal and state laws irreconcilably conflict entails the threshold inquiry of whether there is "newly acquired information" to support a CBE submission. *See* *Albrecht*, 139 S. Ct. at 1679 ("[M]anufacturers cannot propose a change that is not based on reasonable evidence."). If the answer is no, then the state law claim is preempted. *See, e.g.*, *Knight v. Boehringer Ingelheim Pharm., Inc.*, 984 F.3d 329, 332 (4th Cir. 2021) (finding, post-*Albrecht*, that because the manufacturer did not have "newly acquired information" to unilaterally change its label, the state law claim is preempted). If the answer is yes, then the Court considers whether there

is clear evidence that "the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Albrecht*, 139 S. Ct. at 1672. *See also In re Taxotere (Docetaxel) Prod. Liab. Litig.*, No. 16-17039, —— F.Supp.3d ——, —— – ——, 2020 WL 7480623, at *9–10 (E.D. La. Dec. 18, 2020) (proceeding to the clear evidence question promulgated in *Albrecht* after finding that the manufacturer had newly acquired information to support a CBE change). If the answer to the clear evidence question is yes, then the state law claim is preempted. As such, the preemption framework provides two potential avenues by which Defendants may establish that federal and state laws irreconcilably conflict. The Court analyzes each below.

i. "Newly Acquired Information" to Support a CBE Label Change

As previously mentioned, the Supreme Court in *Albrecht* made clear that, in the ordinary case, a drug manufacturer will not be able to show actual conflict between federal and state law because of the availability of the CBE regulations. 139 S. Ct. at 1679. This case, however, is not an ordinary case. Unlike in *Wyeth* where the FDA and manufacturer "gave no more than passing attention to the issue," 555 U.S. at 572, 129 S.Ct. 1187, the FDA and manufacturers here have devoted considerable time and attention to the specific safety issue raised by Plaintiffs.[5] As such, the Court deems it appropriate to consider the question of whether there is "newly acquired information" to support a CBE submission against the backdrop of the FDA's years-long attention to, and evaluation of, the pancreatic safety of incretin-based drugs.

5 The Court incorporates herein its prior analysis in 2015 that this case "is clearly distinguishable from the facts presented and found insufficient for preemption in *Levine* and *Gaeta*." (Doc. No. 1539 at 19.)

a. FDA Monitoring of Incretin-Based Therapies

By way of background, the FDA approved Byetta (exenatide) in April 2005 and Januvia and Janumet (sitagliptin) in 2006 and 2007. The FDA has monitored and reviewed the safety of incretin-based therapies with respect to pancreatic cancer for several years. In 2009, the FDA reviewed its adverse event reporting system database for incidences of pancreatic cancer associated with exenatide, sitagliptin, and other anti-diabetics. (Doc. No. 3594-3 at 206–07.) Upon review, the FDA found that "little inference for risk is appreciated from review of spontaneous reports of pancreatic cancer" and concluded that "a causal association between exposure to one of these agents and pancreatic cancer is indeterminate at this time." (*Id.* at 213–14.) Based on its conclusion, the FDA did not make any labeling recommendations for exenatide or sitagliptin. (*Id.* at 214.) A month later, in January 2010, the FDA approved Victoza (liraglutide).

In March 2013, the FDA issued a drug safety communication directly related to the pancreatic safety of incretin mimetics. (*Id.* at 219.) In the communication, the FDA announced that it was "investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes." (*Id.*) It explained that it would "obtain and evaluate" the information underlying the reports, as well as "evaluate all available data to further understand this potential safety issue." (*Id.*) The FDA also stated that it had not concluded that incretin mimetics cause or contribute to the development of pancreatic cancer, and advised health care professionals to continue following the prescribing recommendations in the drug labeling. (*Id.*)

***6** In June 2013, as part of its review of the risk of pancreatic cancer associated with incretin mimetics and "to gather and share additional information," the FDA participated in the National Institute of Diabetes and Digestive Kidney Diseases and National Cancer Institute's workshop on Pancreatitis-Diabetes-Pancreatic Cancer. (*Id.*) At the workshop, an FDA official reaffirmed that adverse event data was "less suitable for detecting relatively more common events with long latency periods" such as pancreatic cancer. (Doc. No. 1163-4 at 94.) Another FDA official commented that incretin-based drugs were not associated with "[o]vert pancreatic toxicity or pancreatic neoplasms ... that would indicate a risk to human safety." (*Id.* at 89.) The FDA official shared that it "issued a post-marketing requirement (PMR) on the sponsors of exenatide, liraglutide, and sitagliptin to conduct a pancreatic toxicology study in a rodent model of T2D[6]," and that none of the three studies that met the PMR criteria "definitively demonstrated a treatment-related adverse effect on exocrine histology or proliferation." (*Id.*)

6 T2D is an abbreviation for Type 2 diabetes. (Doc. No. 1163-4 at 89.)

Notably, in February 2014, the FDA published an article in the *New England Journal of Medicine* ("NEJM") titled, "Pancreatic Safety of Incretin Mimetics — FDA and EMA Assessment" ("Assessment"). (Doc. No. 3594-3 at 2.) The Assessment was authored by four FDA officials and members of the European Medicines Agency (EMA). (*Id.* at 4.) According to the Assessment, the FDA independently completed its "comprehensive evaluation[ ] of a safety signal arising from post-marketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs." (*Id.* at 3.) The FDA's comprehensive evaluation included re-evaluation of more than 250 toxicology studies, as well as a review of clinical safety databases and the results of cardiovascular outcome trials in patients with type 2 diabetes who were treated with incretin-based drugs. (*Id.*)

As to the relevance of adverse event reports of pancreatic cancer, the Assessment confirmed that "there are inherent limitations to the ability to establish causal relationships" due to the high background rates and long latency period of pancreatic cancer, or a possible contribution by type 2 diabetes itself. (*Id.*) Having "explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs," the FDA concluded that "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data." (*Id.*) The FDA further concluded that the "current knowledge is adequately reflected in the product information or labeling" which contained no reference to pancreatic cancer. (*Id.*) [7]

7 The Assessment was updated in June 2014 to amend the description of incretins in the second sentence of the second paragraph. (Doc. No. 3594-3 at 222.) The change is inconsequential to this decision.

Then, in March 2014, the FDA formally responded to a citizen petition from 2012, which called for the withdrawal of Victoza (liraglutide) from the market, claiming in part that Victoza increases the risk of pancreatic cancer and citing FDA Adverse Event Reporting System ("FAERS") data in support. (Doc. No. 3494-4 at 27.) In its response, the FDA reiterated that FAERS data "does not provide strong evidence of risk when the adverse event (i.e., pancreatic cancer) occurs commonly in the background untreated population and has a long latency period." (*Id.*) The FDA further stated that in its review 49 cases recovered from FAERS, it "found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling." Based on these findings, the FDA made no labeling recommendations specific to pancreatic cancer and noted that "[a]ny causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time." (*Id.*)

***7** In September 2014, the FDA again considered the pancreatic safety of incretin mimetics when it evaluated whether to approve Saxenda, a higher dose of liraglutide marketed for weight loss. (Doc. No. 3594-4 at 43.) In the briefing document, the FDA noted that "[r]isk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide ... However, animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association." (*Id.* at 42.) The FDA also referenced its 2014 NEJM Assessment and repeated that it has "explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal" and that such data "do not support pancreatic cancer as an incretin mimetic-mediated event." (*Id.* at 43.) Three months later, the FDA approved the use of a higher dose of liraglutide for weight management, without requiring a pancreatic cancer warning.

Similarly, in June 2017, the FDA prepared a briefing document for a meeting on a proposed new cardiovascular risk reduction indication for liraglutide based on the LEADER study, a randomized double-blinded, placebo-controlled cardiovascular outcomes trial. (Doc. No. 3594-5 at 87, 92.) In addition to assessing liraglutide's cardiovascular safety, LEADER evaluated its pancreatic safety. (*Id.* at 93.) According to the briefing document, "an FDA Oncology consult team has independently reviewed the pancreatic cancer information in LEADER" and "[t]heir overall conclusion is that data generated from LEADER do not appear to substantively alter the original FDA conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer." (*Id.* at 94.) Two months later, the FDA approved the cardiovascular risk reduction indication for Victoza.

Later, in June 2019, the FDA announced that it "approved Victoza (liraglutide) injection for treatment of pediatric patients 10 years or older with type 2 diabetes" making it

"the first non-insulin drug approved to treat type 2 diabetes in pediatric patients since metformin was approved for pediatric use in 2000." (Doc. No. 3594-4 at 576.) Indeed, for the last several years, the FDA has approved new incretin-based medications without requiring a reference to pancreatic cancer in their labels. Notably, the FDA has also approved various labeling changes for Defendants' drugs since their initial approval—the most recent of which was in June 2019 for liraglutide, August 2019 for sitagliptin, and February 2020 for exenatide. Despite their close monitoring and comprehensive evaluation of the pancreatic safety of incretin-based therapies, the FDA has never required Defendants to include a pancreatic cancer warning in their drug labeling.

Guided by *Wyeth v. Levine* and the record before it in November 2015, this Court granted Defendants' first motion for summary judgment based on preemption, holding that "Defendants have demonstrated by clear evidence that the FDA would have rejected a reference to pancreatic cancer in the product labeling during the time in which Plaintiffs' claims accrued." (Doc. No. 1539 at 34.) In so holding, the Court relied on the February 2014 NEJM Assessment and the FDA's March 2014 formal rejection of the citizen petition requesting withdrawal of Victoza—both of which "falls squarely within the FDA's congressionally delegated authority to regulate the safety of prescription drugs" (*id.* at 25), and communicated that a causal association between incretin-based drugs and pancreatic cancer is not supported by the FDA's review of the data (*id.* at 18–19).

Although the Court's decision was appealed, the Ninth Circuit did not consider the Court's preemption findings and remanded the case for other reasons. *In re Incretin-Based Therapies Prod. Liab. Litig.*, 721 F. App'x at 581–82. And as *Albrecht* did not create new preemption law, but rather, merely elaborated on *Wyeth*, the Court reaffirms its 2015 findings that the record at that time:

> ***8** establishe[d] the FDA has specifically considered pancreatic cancer risk, commented publicly on the adequacy of drug labeling, and maintained its position that scientific evidence of a causal association between incretin mimetics and pancreatic cancer is indeterminate. Because an indeterminate causal association falls below the federal regulatory standards required for labeling changes, clear evidence exists that the FDA would have rejected a reference to pancreatic cancer in product labeling.

(Doc. No. 1539 at 2.) Consequently, with this particular regulatory and procedural backdrop in mind, the Court considers whether the supplemented record before it shows that Defendants had newly acquired information sufficient to support a CBE submission for a pancreatic cancer warning.

b. Purported "Newly Acquired Information"

The CBE regulation "permits drug manufacturers to change a label without prior FDA approval if the change is designed to 'add or strengthen a warning' where there is 'newly acquired information' about the 'evidence of a causal association' between the drug and a risk of harm." *Albrecht,* 139 S. Ct. at 1673 (alterations omitted) (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). "Newly acquired information" is defined as

> data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 314.3. Again, a manufacturer "cannot propose a change that is not based on reasonable evidence." *Albrecht*, 139 S. Ct. at 1679. The proposed change must be based on "reasonable evidence of causal association" between a drug and a clinically significant hazard. 21 C.F.R. §§ 201.57(c)(6)(i); 314.70(c)(6)(iii)(A). The FDA's regulations are intended to ensure that a label's wording is scientifically valid, and designed to prevent over-warning, exaggeration

of risk, and inclusion of speculative or hypothetical risks that could discourage appropriate use of a beneficial drug. *Id.* at 1673. In support of their contention that Defendants failed to provide material new safety information to the FDA, Plaintiffs point to the following information.

Sitagliptin

For sitagliptin, Plaintiffs point to: (1) Health Canada's 2014 signal assessment, (2) an "imbalance" in clinical trials, (3) a 2014 amendment to the TECOS randomized clinical trial study protocol, and (4) nonclinical studies involving desfluorositagliptin.

To begin, the Court finds that Health Canada's signal assessment does not constitute "newly acquired information" under FDA regulations because it does not "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3. Rather, the Health Canada publication is akin to the FDA's 2013 drug safety communication. Both alerted the public and health professionals about the potential safety issue "that incretin-based therapies could possibly be associated with an increased risk of developing pancreatic cancer." (Doc. No. 3594-4 at 624). Like the FDA's safety communication, the Health Canada article announced that "Canada has initiated an epidemiological [8] study through the Drug Safety and Effectiveness Network (DSEN) to assess the potential association between pancreatic cancer and incretin-based therapies and will continue its ongoing monitoring of this potential safety issue." (*Id.* at 625.)

8 "Epidemiological studies examine the pattern of disease in human populations." *Joiner*, 522 U.S. at 144 n.2, 118 S.Ct. 512.

***9** Moreover, the publication was a preliminary assessment and did not rely on information different to that already considered by the FDA's comprehensive review. (*Id.* at 583 (Dr. Goldkind, former FDA Acting Division Director, noting that the data referenced in the publication contains only "a portion of a much more exhaustive review that the FDA did and that much of their data in fact came from the FDA.").) Furthermore, Health Canada later completed its review in 2016 and "concluded that there is not enough evidence at this time to confirm a link between incretin-based therapies and pancreatic cancer." (*Id.* at 633.) As such, the Court does not find that the 2014 Health Canada preliminary assessment amounts to reasonable evidence of a causal link, and is therefore not "newly acquired information" that would have been material to the FDA's investigation or support a CBE submission. *See* *Albrecht*, 139 S. Ct. at 1679; *see also* *Ridings v. Maurice*, 444 F. Supp. 3d 973, 994 (W.D. Mo. 2020) (noting that "[f]oreign drug labeling is the product of different and distinct regulatory standards and decisions" and "warnings approved for a foreign label are not in and of themselves newly acquired evidence").

Plaintiffs also allege that Merck failed to disclose certain pancreatic cancer incidents in its sitagliptin clinical trials, "thereby creating the false impression of an equal number of [pancreatic cancer] cases in sitagliptin and comparators." (Doc. No. 3721 at 33.) The record shows, however, that Merck informed the FDA about its exclusion of certain studies in the pooled data analysis to which Plaintiffs refer, and explained to the FDA that the studies were excluded because they included patients with renal failure receiving lower doses of sitagliptin, or because data was otherwise lacking. (Doc. No. 3824-2 at 29.) No record evidence, expert or otherwise, supports Plaintiffs' allegations of misrepresentation of this data. Consequently, the Court discerns no basis to find that such assertions amount to "newly acquired information." *See* 21 C.F.R. § 314.3.

Plaintiffs additionally contend that Merck misled the FDA about the results of the TECOS study because it included three pancreatic cancer events that occurred more than 28 days after the patient's use of the study drug, but before the TECOS protocol was amended to require collection of such events. (Doc. No. 3721 at 41–42.) Plaintiffs' assertion that "there is no indication Merck ever flagged any of these issues for the FDA" is incorrect. A 2014 letter from Merck to the FDA shows that Merck informed the FDA about the TECOS protocol amendment and provided related information, including that for the three pancreatic cancer cases counted. (Doc. No. 3824-2 at 31.) The FDA was therefore aware of any potential amendment-related deficiencies in the study. Moreover, none of Plaintiffs' experts have called into question the pancreatic cancer results from the TECOS study. Accordingly, because Merck previously made this information available to the FDA, it does not constitute "newly acquired information". *See* 21 C.F.R. § 314.3.

Lastly, Plaintiffs assert that Merck should have disclosed to the FDA its studies involving desfluorositagliptin, a chemical analog to sitagliptin. The Court disagrees. The drug at issue here is sitagliptin—not desfluorositagliptin. Moreover, desfluorositagliptin is not on the market and not available for clinical use. None of the plaintiffs in this litigation consumed desfluorositagliptin or claimed that it caused them injury. While Plaintiffs suggest that Merck should have provided the FDA with studies relating to desfluorositagliptin, there is no evidence that studies involving desfluorositagliptin necessarily amount to reasonable evidence that sitagliptin causes pancreatic cancer. In fact, a former Merck research scientist involved in desfluorositagliptin studies, testified that although the two drugs have similar properties, "[t]hey are by nature two different molecules." (Doc. No. 3824-2 at 44.) Without more, the Court declines to find that non-human studies pertaining to a drug different in molecular nature to sitagliptin amount to reasonable evidence that sitagliptin causes pancreatic cancer.

***10** And as to Plaintiffs' reference to a 2008 mouse study involving desfluorositagliptin, that study is publicly available online, and in any event, does not reveal apparent pancreatic safety concerns with respect to desfluorositagliptin. (Doc. No. 3824-2 at 53–54.) Consequently, the Court does not find that nonclinical studies involving desfluorositagliptin constitute newly acquired information that would support a CBE submission for sitagliptin.

For the foregoing reasons, the Court finds that Merck does not have safety information that reveals risks of a different type or greater severity or frequency than previously included in submissions to FDA, and thus, does not have "newly acquired information" on which to base a CBE submission. *See* 21 C.F.R. §§ 314.3, 314.70. As Merck cannot unilaterally change sitagliptin's drug label to include a pancreatic cancer reference, Plaintiffs' state law failure-to-warn claims against Merck is preempted. *See* *Albrecht*, 139 S. Ct. at 1679.

Exenatide

For exenatide, Plaintiffs point to: (1) Amylin's claim that a 14-week baboon study found no "PanIN" [9] lesions; (2) Amylin's internal presentation of pancreatic cancer events in its clinical trials; and (3) "compromised data collection" in the EXSCEL cardiovascular outcome randomized clinical trial.

9 "PanIN" refers to pancreatic intraepithelial neoplasia, which are lesions that most commonly occur in the smaller pancreatic ducts. (Doc. No. 3586-5 at 362.) The presence of PanINs are common, especially in individuals above the age of 50. (*Id.*) Pancreatic ductal adenocarcinoma is believed to arise from certain PanIN lesions that have acquired a series of additional mutations. (*Id.*)

As to the 14-week baboon study, Plaintiffs allege that Amylin falsely claimed to the FDA and the medical community that "no dysplastic lesions, pancreatic intraepithelial neoplasia (PanIN), or lesions resembling pancreatic cancer were observed in any pancreatic specimen examined at baseline or after treatment in either animal group." (Doc. No. 3721 at 33.) Amylin's position that there were no PanIN lesions observed in a 14-week baboon study is based on a peer-reviewed published article of that study. Notably, the article was made available to the FDA, and Plaintiffs do not contend otherwise. Instead, Plaintiffs maintain that Amylin misrepresented the baboon study, and in support, cite a one-page document that lists "PanIN" and "noPanIN" counts for "exenetide [sic]" and "no exenetide [sic]" groups. (Doc. No. 3721-9 at 2.) Other than numbers and labels, however, the document contains no explanation as to the data's source, context, or meaning. It also makes no mention of any findings based on this data. Without more, the Court cannot evaluate whether, and therefore does not find that, this information amounts to newly acquired information.

Additionally, to the extent that Plaintiffs argue that their expert's re-analysis of the slide images finding PanINs in exenatide-treated animals amounts to newly acquired information, the Court disagrees. This expert report was generated in preparation for litigation and is not supported by published research. *Roberto v. Boehringer Ingelheim Pharm., Inc.*, No. CPLHHDCV166068484S, 2019 WL 5068452, at *19 (Conn. Super. Ct. Sept. 11, 2019) ("[T]he court is unaware of any authority for the proposition that expert testimony at trial, unsupported by any published research, can constitute newly acquired information."); *accord Adkins v. Boehringer Ingelheim Pharm., Inc.*, No. X03HHDCV1606065131S, 2020 WL 1890681, at *9 (Conn. Super. Ct. Mar. 13, 2020) (declining to find that a "statement from a single scientist" constitutes newly acquired information "at least until that statement becomes part of a peer-reviewed article or finds other forms of corroboration"). The Court therefore finds that one unpublished and litigation-driven animal study "does not make a risk 'apparent' or

otherwise constitute 'reasonable evidence of association.' " *McGrath*, 393 F. Supp. 3d at 170.

***11** Plaintiffs also contend that Amylin's summary of the clinical data in its Periodic Benefit-Risk Evaluation Report (PBRER) to the FDA is misleading. In support, Plaintiff's cite an internal study summary that they believe was the source of Amylin's PBRER summary. However, the PBRER and internal summaries analyzed different data sets. Unlike the internal summary, the PBRER separated the data for exenatide once-weekly and exenatide twice-daily. The total number of pancreatic cancer events in exenatide-treated patients, however, is the same in both summaries. The Court therefore declines to find the PBRER submission misleading. And in any event, Plaintiffs do not dispute Amylin submitted all clinical trial data to the FDA. Thus, this claim does not demonstrate newly acquired information.

In addition, Plaintiffs argue that Amylin manipulated the results in a 2014 published article that was later submitted to the FDA by cherry-picking the clinical data on which the article is based. (Doc. No. 3721 at 50–51.) Other than argument, however, Plaintiffs offer no evidence that would allow the Court to conclude that the researchers' decision to apply the inclusion criteria it chose for its analysis was inappropriate or without scientific basis. Moreover, the article clearly states the researchers' methodology, inclusion criteria, data, conclusion, and perceived analytical limitations. All of this information was therefore available for the FDA's scrutiny and review. Thus, the Court does not find this to be newly acquired information.

Next, Plaintiffs assert that Amylin's EXSCEL randomized clinical trial results are "the product of compromised data collection" because the study protocols were deficient and because some individuals in the placebo group who developed pancreatic cancer were taking other incretin mimetics. (Doc. No. 3721 at 51–53.) Neither argument is availing. First, the EXSCEL study protocols were submitted to and approved by the FDA. (Doc. No. 3824-2 at 71–74.) Thus, the Court declines to find that such protocols were deficient. Second, although Plaintiffs correctly note that three placebo patients were taking sitagliptin, "concomitant use of DPP-4 inhibitors [was] permitted." (*Id.* at 72.) As to the placebo patient who was taking liraglutide, and therefore should have been excluded based on the exclusion criteria, there is no indication that this information was not made available for the FDA's scrutiny and review. Indeed, Plaintiffs do not contend that Amylin failed to submit all EXSCEL data to the FDA. Rather, Plaintiffs attack, without expert evidence, the wisdom and reliability of the EXSCEL protocol, reporting, and results—arguments irrelevant to whether Amylin failed to submit newly acquired information that could support a CBE label change.

Accordingly, for the foregoing reasons, the Court finds that Amylin does not have safety information that reveals risks of a different type or greater severity or frequency than previously included in submissions to FDA, and thus, does not have "newly acquired information" on which to base a CBE submission. *See* 21 C.F.R. §§ 314.3, 314.70. As Amylin cannot unilaterally change exenatide's drug label to include a pancreatic cancer reference, Plaintiffs' state law failure-to-warn claims against Amylin is preempted. *See* *Albrecht*, 139 S. Ct. at 1679.

Liraglutide

For liraglutide, Plaintiffs point to: (1) a pancreatic tumor report in a weight management trial, (2) five animal studies, and (3) Humedica, an observational study that estimated the background rate of pancreatic cancer in a group of patients with Type 2 diabetes.

To start, Plaintiffs argue that Novo failed to disclose a pancreatic tumor event from a weight management trial. (Doc. No. 3721 at 15.) However, this tumor was benign, and therefore cannot amount to reasonable evidence of a causal link. And in any event, the record shows that Novo informed the FDA about this event. (Doc. Nos. 3824-3 at 26, 32.) Apart from the benign tumor, Plaintiffs do not claim that Novo failed to disclose any other pancreatic cancer events in its clinical trials. Rather, Plaintiffs take issue with how Novo chose to summarize and report such clinical data in the 2018 Periodic Safety Update Report ("PSUR") submitted to the FDA. Specifically, Plaintiffs cite perceived inconsistencies between the 2018 PSUR and Novo's 2017 internal "Surveillance Report." (Doc. No. 3721 at 41.) However, the record shows that the summaries had different inclusion and exclusion criteria: the 2018 PSUR included "all treatment-emergent pancreatic neoplasms in exploratory/confirmatory trials," (Doc. Nos. 3721-23; 3824-3 at 20), while the 2017 Surveillance Report included "events/cases from all ongoing and completed" trials, (Doc. No. 3721-25 at 3). The context for the numbers reported in the PSUR is plainly stated in the document. As such, the Court

declines to find that Novo misrepresented or omitted certain data.

***12** Moving to the animal studies, Plaintiffs contend that Novo failed to provide evidence from five animal experiments. (Doc. No. 3721 at 34.) In particular, Plaintiffs point to a 2001 ZDF rat study which contained data that regeneration and acinar hyperplasia was observed in some of the rats. However, Plaintiffs do not explain how this data constitutes reasonable evidence of a causal association. There is no expert opinion that these observations provide reasonable evidence of a causal link, and none of the rats in the study developed pancreatic cancer. To the extent that Plaintiffs focus on the observed acinar hyperplasia, the Court notes that similar observations have been made in other animal studies, including those evaluated, and found insufficient for a causal link, by the FDA. (Doc. No. 3594-3 at 4.) Moreover, the evidence indicates that acinar hyperplasia is a benign increase in size of normal acinar cells that is "[r]eported in up to 44% of pancreata," and there is "[n]o evidence of progression to carcinoma" related thereto. (Doc. No. 3824-4 at 23.) Without more, the 2001 ZDF study does not constitute reasonable evidence of causal association, and thus, falls short of the requisite "newly acquired information" for a CBE label change.

Plaintiffs also raise a 2012-2013 post-hoc exploratory analysis of the effect of liraglutide on pancreatic duct glands (PDGs), which Novo concedes it did not submit to the FDA. (Doc. No. 3721 at 34, 37–38.) Novo explains that while it submitted the results of the primary study to the FDA, it did not submit the post-hoc secondary PDG analysis because its results were never finalized. The record supports Novo's explanation. A researcher on this study testified in her deposition that the research team determined that "the secondary analysis didn't have any results that were valid so it can't be reported." (Doc. No. 3594-5 at 85.) And after reviewing the study's nearly 2,000 digital slides and draft analysis, defense expert Dr. Sarah Thayer identified various deficiencies in the study and concluded that "[g]iven the lack of scientific rigor and study weaknesses, this data would not be sufficient to reach any meaningful conclusions."[10] (*Id.* at 274.) There being nothing to undermine the team's determination that the secondary study was flawed, the Court does not find that it amounts to "newly acquired evidence" under the CBE regulation. *See, e.g.*, *Ridings*, 444 F. Supp. 3d at 996 (declining to find that a computer testing "that simply did not pan out" constitutes newly acquired information); *McGrath*, 393 F. Supp. 3d at 169 (noting that the CBE regulations contemplate "*well-grounded* scientific evidence") (emphasis in original).

10 Although Plaintiffs filed a motion to exclude against Dr. Thayer, their motion does not challenge this portion of her report.

Next, Plaintiffs claim that Novo should have informed the FDA about two studies where a mouse from each study was observed to have inflamed pancreas. (Doc. No. 3721 at 35–36.) The objectives of these studies, however, did not concern the pancreatic safety of liraglutide. One study's aim was "[t]o evaluate the effect of liraglutide in prevention of diabetic nephropathy defined as reduction in albuminuria and mesangial expansion." (Doc. No. 3824-3 at 34.) And the other's aim was "to evaluate effects of treatment with combination of FGF21 and the GLP-1 agonist, liraglutide on body weight, body composition and on bone mineralization in DIO mice." (*Id.* at 36.) Because the studies assessed data different from liraglutide's pancreatic safety, the Court declines to find that the pancreatic findings in these two mice serve as reliable information amounting to reasonable evidence of a causal link between liraglutide and pancreatic cancer. And there is no expert evidence for the Court to determine otherwise. Moreover, there is scientific literature recognizing that spontaneous pancreatic findings occur in the normal background rate for rodents, regardless of whether they have been exposed to treatment. (Doc. No. 3594-5 at 303.) As such, the Court does not find that these animal studies constitute newly acquired information for purposes of the CBE regulations.

Plaintiffs additionally point to a study, which examined the effect of combining a certain medication with liraglutide on glucose levels in ZDF rats. (Doc. No. 3824-3.) While some rats died and developed illness, the researchers did not find the events to be linked to liraglutide or the medication with which it was combined. (Doc. No. 3721-16.) Rather, the researchers suspected that the events may have been attributed to a particular test conducted as part of the study. (*Id.*) Further, none of the rats that died or became ill were treated with liraglutide alone. Thus, without more, the Court does not find that this study reflects reasonable evidence of a causal link and is therefore insufficient for a CBE label change.

***13** Lastly, Plaintiffs assert that Novo failed to provide data from the Humedica study, an internal observational study that attempted to estimate the incident rate of pancreatic cancer among a number of patients with type 2 diabetes and risk factors similar to some extent to those in Novo's LEADER

clinical trial. (Doc. No. 3721 at 38–40.) Contrary to Plaintiffs' contention that Novo "buried" the data, however, the evidence shows that Novo disclosed the Humedica study to the FDA on November 2015. (Doc. No. 3824 at 42 n.83). The study is publicly posted on the FDA's website, and the page clearly states, "Information provided by (Responsible Party): Novo Nodisk A/S." (*Id.*) Thus, the Court finds that the Humedica study is not newly acquired information.

Plaintiffs also take issue with Novo's decision to represent, in its FDA briefing document for the LEADER Advisory Committee, an expected background rate of pancreatic cancer different from that estimated in the Humedica study. (Doc. No. 3721 at 38.) Novo asserts that it chose not to rely on the Humedica background estimate of 0.036 events per 100 patient years because comparing data from this observational study to the LEADER clinical trial would not be reliable.[11] As noted by the Humedica study's author, the particular methodology employed "resulted in notably lower malignancy rates" compared to other studies and suggested that their algorithm "may have less complete capture of malignancy diagnoses." (Doc. No. 3721-21 at 27.) Additionally, none of the patients in the Humedica observational study actually took liraglutide, and thus, its direct bearing on the pancreatic safety of liraglutide is limited. As such, instead of relying on the Humedica background rate, Novo endorsed in its FDA briefing document, a predicted background rate range of 0.05 to 0.08 events per 100 patient years—a range based on three independent, peer-reviewed analyses. (Doc. No. 3824 at 43.) There is no evidence that doing so was unreasonable or inappropriate. Without more, the Court rejects Plaintiffs' allegation that Novo deceived the FDA as to the expected background rate in LEADER.

11 Indeed, Plaintiffs' own expert testified that there are limitations with comparing incident rates in a clinical trial to incident rates in an observational study. (Doc. No 3824-3 at 12.) For example, he noted that the patients in the two cohorts may be different, and the way pancreatic cancer is defined or ascertained may also be different between the two studies. (*Id.* at 12–13.)

Accordingly, for the foregoing reasons, the Court finds that Novo does not have safety information that reveals risks of a different type or greater severity or frequency than previously included in submissions to FDA, and thus, does not have "newly acquired information" upon which to base a CBE submission. *See* 21 C.F.R. §§ 314.3, 314.70. As Novo cannot unilaterally change liraglutide's drug label to include a pancreatic cancer reference, Plaintiffs' state law failure-to-warn claims against Novo is preempted. *See* *Albrecht*, 139 S. Ct. at 1679

c. Newly Acquired Information Conclusion

As a final note, it bears repeating that the FDA's CBE regulations are designed to ensure that only scientifically justified information is provided in the labeling for an approved product. *See* *Albrecht*, 139 S. Ct. at 1673 (citing Supplemental Application Proposing Labeling Changes for Approved Drugs, Biologies, and Medical Devices, 73 Fed. Reg. 2851 (Jan. 16, 2008)). The regulations reflect the FDA's cautious approach to drug labeling, recognizing that "exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug ... or decrease the usefulness and accessibility of important information by diluting or obscuring it." *Id.* *See also McGrath*, 393 F. Supp. 3d at 169 (noting that "the FDA prefers a more cautious approach" to its CBE regulation "because labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance"). As discussed above, the FDA, through its own evaluation and armed with information from Defendants and other sources, considered the specific issue raised by Plaintiffs in this case: the pancreatic safety of incretin mimetics. At no point in its years-long monitoring of these drugs did the FDA require Defendants or any other manufacturer of incretin-based therapies to add a pancreatic cancer warning to its labels.

***14** Quite the contrary, the FDA has published its findings regarding the pancreatic safety of incretin mimetics, commented on the adequacy of the drug labeling, and maintained its position that scientific evidence of a causal association between incretin-based therapies and pancreatic cancer is indeterminate. The FDA's finding of an indeterminate causal link between pancreatic cancer and incretin mimetics is not reasonable evidence of a causal association. *See* *Ridings*, 444 F. Supp. 3d at 992 ("studies concluding that it 'remains unknown' whether a drug is linked to a particular adverse reaction or risk or that 'further studies are required to address possible clinical consequences' do not constitute reasonable or well-grounded scientific evidence of "clinically significant adverse effects" under

the CBE regulation.") And as previously analyzed, none of the purported new safety information reflects well-grounded scientific evidence of causal association that would have made the risk of pancreatic cancer apparent to Defendants. *See* *id.* at 1677 ("[W]hen the risks of a particular drug become apparent, the manufacturer has a duty to provide a warning that adequately describes that risk.") (citation and alteration omitted). Because Defendants do not have newly acquired information to support a CBE label change, they cannot unilaterally change their product label. *See* *id.* at 1679 ("[M]anufacturers cannot propose a change that is not based on reasonable evidence.") Consequently, the relevant federal and state laws in this case "irreconcilably conflict." *Albrecht*, 139 S. Ct. at 1679. Accordingly, the Court will grant Defendants' motion for summary judgment based on preemption on this basis.

ii. Clear Evidence that the FDA Would Not Approve the Label Change

Although unnecessary, the Court further finds that Defendants established clear evidence that the FDA would not approve a label change. As laid out in the preceding section, the FDA has been monitoring the pancreatic safety of incretin mimetics for over a decade, and Defendants have disclosed to the FDA all material information concerning the relationship between their drugs and pancreatic cancer. *See supra* § IV.A.2.i. Thus, the Court finds that Defendants fully informed the FDA of the justifications for a pancreatic cancer warning. *Cf. In re Taxotere (Docetaxel) Prod. Liab. Litig.*, No. 16-17039, —— F.Supp.3d at ——, 2020 WL 7480623, at *11 (finding that the FDA was not "fully informed" because its limited knowledge of the risk and repeated request for the manufacturer to provide additional information and analysis signaled to the Court that the manufacturer was not "making an 'earnest attempt' to keep the FDA informed of the possible need for a stronger warning.") (citations omitted).

Turning to the remaining question of whether the FDA informed the manufacturers that it would not approve a label change, Plaintiffs primarily argue that Defendants have not pointed to any agency action carrying the force of law to establish preemption. (Doc. No. 3721 at 24.) The Court disagrees. *Albrecht* "make[s] only the obvious point that, *whatever the means* the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated." 139 S. Ct. at 1679 (emphasis added). Moreover, this Court considered this exact question in 2015 and found that the FDA's 2014 Assessment and formal rejection of the citizen petition requesting the withdrawal of Victoza communicated the FDA's official position that assertions concerning a causal association between pancreatic cancer and incretin-based drugs were inconsistent with the current data, and that such communications "both fall within the FDA's congressionally delegated regulatory authority." (Doc. No. 1539 at 26.)

Specifically, this Court reasoned:

> The FDA's review of pancreatic safety data of the drugs at issue falls squarely within the FDA's congressionally delegated authority to regulate the safety of prescription drugs. The Assessment exemplifies the FDA's approach in discharging its regulatory duties. Four FDA officials authored the Assessment, and the Assessment is identified as coming from the FDA's Office of New Drugs, Center for Drug Evaluation and Research. Additionally, the Assessment is written from the FDA's perspective and lacks the disclaimer required when publications of FDA employees do not necessarily reflect the opinions of the agency. (*See* Doc. No. 1163–4 at 98) (noting all non-assigned FDA-related articles or speeches must include a disclaimer stating the article "reflects the views of the author and should not be construed to represent FDA's views or policies"). Plaintiffs' regulatory expert acknowledges the Assessment represents the FDA's official position regarding pancreatic safety. (Doc. No. 1163–3 at 85:1–16.) Similarly, responding to citizen petitions is within the FDA's regulatory authority. The Victoza citizen petition rejection was written by the Director of the FDA's Center for Drug Evaluation and Research, and constitutes the FDA's official response to the request to withdraw Victoza from the market.

(Doc. No. 1539 at 24–25.) As Plaintiffs' arguments to the contrary remain unavailing, the Court reaffirms and elaborates upon its prior findings.

***15** To begin, although the question of disapproval method was not before it, the Supreme Court provided examples of how the FDA may communicate its disapproval of a warning, including (1) by means of notice-and-comment rulemaking setting forth labeling standards (2) by formally rejecting a warning label that would have been adequate under state law, or (3) with other agency action carrying the force of

law. *Albrecht*, 139 S. Ct. at 1679. Plaintiffs argue that the 2014 Assessment does not constitute agency action carrying the force of law because it is an informal communication and cites 21 C.F.R. § 10.85(k) in support. That regulation states that an FDA employee's written statement constitutes "an informal communication" and "does not *necessarily* represent the formal position of FDA." 21 C.F.R. § 10.85(k) (emphasis added.) As such, by its own text, the regulation contemplates that certain employee-written statements may be representative of the FDA's formal position. The 2014 Assessment is such a statement.

Moreover, the Court again notes that the FDA has closely monitored a potential safety signal for pancreatic cancer associated with incretin mimetics for several years. (Doc. No. 3594-3 at 11–12.) And in 2013, the agency informed the public and health care professionals that it would be obtaining and evaluating all available data to further understand this potential safety issue. (*Id.* at 219.) That extensive evaluation resulted in the 2014 Assessment, wherein the FDA published its findings concerning the safety profile and labeling of incretin mimetics in the *New England Journal of Medicine*—the top medical journal in the world. Indeed, both parties' regulatory experts agree that the 2014 Assessment is the culmination of the FDA's decision to conduct its own independent, comprehensive evaluation on incretin-based therapies. (*Id.* at 8; Doc. No. 3594-4 at 609.) *See generally* *Albrecht*, 139 S. Ct. at 1672 (explaining that with the enactment of the FDCA, Congress charged the FDA "with ensuring that prescription drugs are 'safe for use under the conditions prescribed, recommended, or suggested' in the drug's 'labeling.' ") (citing 21 U.S.C. § 355(d)). Thus, the Court finds that the 2014 Assessment amounts to "other agency action carrying the force of law." *Id.* at 1679.

The Court also reiterates that the Assessment was authored by four FDA officials, was written from the FDA's perspective, and does not contain the disclaimer that would otherwise be required if the employee-authored publication was not representative of the FDA's position. (Doc. No. 1539 at 24.) The FDA staff manual requires that all non-assigned FDA-related articles or speeches "must include the following disclaimer when published or presented: 'This [article/ speech/presentation/ book chapter] reflects the view of the author and should not be construed to represent FDA's views or policies.' The disclaimer must be prominently displayed as part of its published or presented form." (Doc. No. 3594-3 at 227.) Nowhere in the 2014 Assessment does this disclaimer appear. Instead, the Assessment contains language clearly signifying that the information therein reflects the FDA's views. (*See e.g.*, *id.* at 4 ("*The FDA* and EMA ... *agree* that assertions concerning a causal association .. are inconsistent with the current data" and "*The FDA* and EMA *believe* that the current knowledge is adequately reflected in the product information or labeling.") (emphasis added).) Notably, the parties' regulatory experts confirmed that the Assessment reflects the FDA's position. (*See* Doc. Nos. 3594-3 at 8 (Dr. Fleming: "This represents [sic] FDA's position."); 3594-4 at 609 (Dr. Goldkind: "The Assessment represents FDA's official position.").)

***16** Plaintiffs also reassert that because the Assessment did not reach a final conclusion concerning a causal relationship, it did not inform the drug manufacturers that the FDA would not approve changing the drug's label. (Doc. No. 3721 at 28.) The Court disagrees. The Assessment specifically communicated that the FDA believed that "current knowledge is adequately reflected in the product information or labeling." (Doc. No. 3594-3 at 4.) Otherwise stated, the FDA believed that at the time of the Assessment's publication, the current label for incretin-based drugs—which contained no pancreatic cancer reference—was consistent with the results of FDA's independent and comprehensive evaluation of the drugs' pancreatic safety. (*See id.*) As Defendants' regulatory expert Dr. Goldkind opined, the FDA "specifically has addressed whether the labeling should reference pancreatic cancer and has concluded that it should not." (Doc. No. 3594-4 at 614.) Similarly, Plaintiffs' regulatory expert, Dr. Fleming, testified in his deposition that "[i]t would be a little absurd" for the FDA to allow the addition of a pancreatic cancer warning after its robust and comprehensive evaluation of that specific risk did not yield evidence of causal association. (Doc. No. 3594-3 at 12–13.)

And while the FDA relayed in the Assessment that it would continue to monitor the pancreatic safety of these drugs, the potential for the FDA to reach a different conclusion in the future in light of new scientific evidence or developments does not preclude a finding of preemption now. Rather, as the Court noted in 2015, the FDA's ongoing review of pancreatic safety is more indicative of the evolving nature of drug surveillance, than of the existence of a causal association. (Doc. No. 1539 at 28 (citing Dr. Goldkind's statement that "as a matter of routine practice, FDA continuously monitors every medication for new or evolving information as long as a drug is on the market.").) The Supreme Court acknowledged the same in *Wyeth* when it noted that the CBE regulation

"accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." 555 U.S. at 569, 129 S.Ct. 1187. And as discussed *supra* § IV.A.2.i, the record does not contain "newly acquired information" that would alter the FDA's 2014 conclusion and support a CBE submission.

As further evidence of the FDA's position that it would not approve a pancreatic cancer reference in the drugs' labels, the FDA formally rejected the citizen petition from the Public Citizen's Health Research Group calling for the withdrawal of Victoza. (Doc. No. 3594-4 at 2.) The FDA sent the formal rejection letter a month after the Assessment's publication. The letter included a specific paragraph with the heading "Pancreatic Cancer," which was dedicated to refuting the petitioner's claim that Victoza increases the risk of pancreatic cancer. (*Id.* at 27.) In that section, the FDA explained that it "found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling." (*Id.*)

This letter therefore illustrates that in responding to the Citizen Petition, the FDA considered the same issue raised by Plaintiffs—the risk of pancreatic cancer associated with Victoza—and unequivocally stated that it found no new evidence that would support changes to the drug's label. (*Id.*) *See also Cerveny*, 783 F. App'x at 808 n.9 (noting, post-*Albrecht*, that the manufacturer had a "separate avenue [for establishing preemption]—the FDA's unequivocally having rejected [a] citizen petition advocating for the warning that the [plaintiffs] now assert."). As such, the Court rejects Plaintiffs' contention that "the FDA's rejection of the petition did not inform the manufacturers of incretin mimetics that any proposed pancreatic cancer warning would be rejected." (Doc. No. 3721 at 14.) Accordingly, the Court again finds that the formal rejection of the Citizen Petition falls within the scope of the FDA's congressionally delegated authority. *See* *Albrecht*, 139 S. Ct. at 1679.

The Court also disagrees with Plaintiffs' claim that FDA inaction can never support a preemption finding. While FDA inaction alone is insufficient, the Court notes that pursuant to 21 U.S.C. § 355(o)(4)(a), the FDA has the authority to mandate a label change if it learns of new safety information that should be included in the labeling of a drug. *See also* *Albrecht*, 139 S. Ct. at 1684 (Alito, J., concurring) ("On remand, I assume that the Court of Appeals will consider the effect of § 355(o)(4)(A) on the pre-emption issue in this case."). To date, the FDA has approved several new incretin-based drugs, as well as labeling changes for the medications at issue in this case. None of the approvals required the manufacturers to include a pancreatic cancer reference in the drug labeling. As such, the Court finds that the FDA's silence on this issue is highly relevant to its preemption analysis. *See* *id.* ("if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified ... Section 355(o)(4)(A) is thus highly relevant to the pre-emption analysis.").

***17** Put another way, the Court cannot simply ignore the FDA's demonstrated commitment to actively and continuously monitoring the pancreatic safety of incretin mimetics. For instance, the FDA stated in the Assessment that its "ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future." (Doc. No. 3594-3 at 4.) Consistent with this strategy, the FDA requested an FDA oncology consult team to independently review the pancreatic cancer information in the LEADER cardiovascular outcome trial, and the oncology team concluded that the LEADER data "do not appear to substantively alter the original FDA conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer." (Doc. No. 3494-5 at 94.) Given the specific attention the agency has given to the very matter at issue in this litigation, the Court finds the FDA's approval of new incretin-based drugs, as well as its continued approval of other label changes to the medications at issue —without requiring a pancreatic cancer reference in the label—only further supports the Court's preemption findings. *See* *Ridings,* 444 F. Supp. 3d at 998 (finding that "in light of the known issues and the ongoing give-and-take between [defendant] and the FDA on these issues .. the FDA's continued inaction does represent clear evidence under these facts.").

As such, based on the FDA's Assessment, rejection of the Citizen Petition, and inaction with respect to requiring a pancreatic cancer warning despite its extensive and ongoing evaluation of the issue, the Court finds that the FDA has communicated that it would not approve Plaintiffs'

proposed label change. Consequently, because Defendants fully informed the FDA of the justifications for a pancreatic cancer warning, and the FDA effectively informed them that it would not approve the label change, the relevant federal and state laws in this case "irreconcilably conflict." *Albrecht*, 139 S. Ct. at 1679. Accordingly, the affirmative defense of preemption operates to bar Plaintiffs' claims which accrued prior to the close of the record. For the sake of completeness, however, the Court will also determine the merits of the pending summary judgment motions based on lack of general causation evidence and the *Daubert* motions relating thereto.

B. CAUSATION AND *DAUBERT* MOTIONS

It is well-recognized that general causation is an essential element in products liability cases. *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1172 (N.D. Cal. 2007) (citing *In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1133 (9th Cir. 2002)). The general causation element concerns "whether the substance at issue had the capacity to cause the harm alleged." *In re Hanford Nuclear Reservation Litigation*, 292 F.3d at 1133. And here, as in other complex pharmaceutical products liability cases, general causation requires expert evidence because the existence of a causal relationship between a substance and the particular harm alleged is outside the common knowledge of lay jurors. *See Lust by and through Lust v. Merrell Dow Pharm.*, 89 F.3d 594, 598 (9th Cir. 1996) ("Summary judgment was appropriate since without [expert] testimony, [the plaintiff] offered no evidence of causation, a necessary element of his personal injury action.").

Since the parties' initial expert discovery in 2014, various bench studies, animal experiments, clinical trials, meta-analyses, and observational studies have been conducted. According to Defendants, "to date, not a single researcher, scientific organization, or other body (other than a few of Plaintiffs' experts) has concluded that incretin-based therapies cause pancreatic cancer. Not one." (Doc. No. 3586-1 at 10.) Plaintiffs largely do not contest that their experts stand alone; rather, they maintain that their experts have provided admissible testimony to prove a causal link between incretin mimetics and pancreatic cancer. (Doc. Nos. 3727; 3728 at 10.) Because the outcome of the *Daubert* motions is consequential to the Court's causation analysis, the Court discusses the merits of the parties' respective *Daubert* motions prior to turning to causation.

1) *Daubert* Motions

Federal Rule of Evidence 702 governs the admissibility of expert testimony. Pursuant to Rule 702,

> ***18** [a] witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

Id. "The party offering the expert bears the burden of establishing that Rule 702 is satisfied." *Sundance Image Tech., Inc. v. Cone Editions Press, Ltd.*, No. 02 CV 2258 JM, 2007 WL 935703, at 4 (S.D. Cal. Mar. 7, 2007).

Prior to admitting expert testimony, the trial court must make "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Daubert v. Merrell Dow Pharms., Inc. ("Daubert I")*, 509 U.S. 579, 592–93, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). The trial court acts as a "gatekeeper" by making a preliminary determination of whether the expert's proposed testimony is not only relevant but reliable. *Estate of Barabin v. AstenJohnson, Inc.*, 740 F.3d 457, 463 (9th Cir. 2014). This two-step assessment requires consideration of whether (1) the reasoning or methodology underlying the testimony is scientifically valid (the reliability prong); and (2) whether the reasoning or methodology properly can be applied to the facts in issue (the relevance prong). *Daubert*, 509 U.S. at 592–93, 113 S.Ct.

2786; *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1228 (9th Cir. 1998).

A district court has broad latitude in deciding how to measure reliability and in making the ultimate reliability determination. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 142, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999). In essence, the Court must determine whether the expert's work product amounts to "good science." *Daubert I*, 509 U.S. at 593, 113 S.Ct. 2786. In *Daubert*, the Supreme Court outlined factors relevant to the reliability prong, including (1) whether the theory can be and has been tested; (2) whether it has been subjected to peer review; (3) the known or potential rate of error; and (4) whether the theory or methodology employed is generally accepted in the relevant scientific community. *Id.* at 593–94, 113 S.Ct. 2786. As later confirmed in *Kumho Tire*, "*Daubert's* list of specific factors neither necessarily nor exclusively applies to all experts or in every case. Rather, the law grants a district court the same broad latitude when it decides how to determine reliability as it enjoys in respect to its ultimate reliability determination." 526 U.S. at 141–42, 119 S.Ct. 1167.

Under the relevance or "fit" prong, the testimony must be " 'relevant to the task at hand,' i.e., that it logically advances a material aspect of the proposing party's case." *Daubert v. Merrell Dow Pharms., Inc. ("Daubert II")*, 43 F.3d 1311, 1315 (9th Cir. 1995) (quoting *Daubert I*, 509 U.S. at 597, 113 S.Ct. 2786). Relevance requires opinions that would assist the trier of fact in reaching a conclusion necessary to the case. *See Kennedy*, 161 F.3d at 1230. In general, the *Daubert* analysis focuses on the principles and methodology underlying an expert's testimony, not on the expert's ultimate conclusions. *Daubert I*, 509 U.S. at 595, 113 S.Ct. 2786. However, the Supreme Court has cautioned that "conclusions and methodology are not entirely distinct from one another." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997). As such, "[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Id.*

i. Motion to Exclude Drs. Madigan, Wells, Brown, and Gale

***19** Defendants jointly move to exclude the opinions of Plaintiffs' experts, Drs. Madigan, Wells, Brown, and Gale. (Doc. No. 3586.) Drs. Madigan and Wells are statisticians who evaluated whether statistical evidence of a causal association exists between incretin mimetics and pancreatic cancer. (Doc. No. 3727 at 19.) Dr. Brown is a cellular biologist who evaluated whether it is biologically plausible that incretin-based drugs induce cell proliferation and promote the development of pancreatic cancer. (*Id.* at 50–51.) Dr. Gale is an oncologist who evaluated the question of whether incretin-based therapies cause or contribute to pancreatic cancer. (*Id.* at 73.) The Court discusses the merits of Defendants' motion to exclude these experts in turn.

a. Dr. Madigan

Dr. Madigan is one of Plaintiffs' two biostatistics experts. In 2015, he conducted a combined meta-analysis of clinical trial data for sitagliptin, exenatide, and liraglutide, and submitted a report, concluding that there is "positive evidence of a causal association between incretin exposure and pancreatic cancer, with an estimated risk of 88%" but cautioned that due to lack of power, there is substantial "uncertainty around the estimate." (Doc. No. 3586-10 at 35.) Dr. Madigan submitted a supplemental report in October 2019. (*Id.* at 55.) This report concerned liraglutide only.

Plaintiffs concede that they "do not intend to offer Dr. Madigan for purposes of establishing a causal association (as it relates to Merck's and Amylin's product)." (Doc. No. 3727 at 19–20.) Instead, with respect to sitagliptin and exenatide, Plaintiffs offer only Dr. Madigan's testimony that the available data for these drugs " 'just shows a lot of uncertainty' and is not evidence the product is safe." (*Id.* at 20.) Dr. Madigan, however, has not reviewed all available clinical trial data and literature for sitagliptin and exenatide since his 2015 report. Plaintiffs themselves acknowledge that "[s]ince that time, the landscape for incretins changed." (*Id.* at 19.) Yet, Plaintiffs did not ask Dr. Madigan to update his prior analysis, and instead asked him to update his analysis of liraglutide only. (Doc. Nos. 3586-4 at 82, 104; 3586-10 at 55, 58). Because Dr. Madigan has not updated his 2015 report as to sitagliptin and exenatide, and has not considered all available clinical data and peer-reviewed literature relating

thereto, his testimony that the data for these medications shows a lot of uncertainty and is not evidence of their safety is misleading and not based upon scientific methodology. Consequently, the Court finds that Dr. Madigan's testimony is unreliable and not helpful to the jury. *See* *Joiner*, 522 U.S. at 146, 118 S.Ct. 512 ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."); *Moses v. Payne*, 555 F.3d 742, 756 (9th Cir. 2009) ("Under Rule 702, expert testimony is helpful to the jury if it concerns matters beyond the common knowledge of the average layperson and is not misleading."). Accordingly, the Court excludes Dr. Madigan's outdated and unfounded opinions as to sitagliptin and exenatide.

***20** As to liraglutide, Dr. Madigan concluded that "[t]o a reasonable degree of scientific certainty, the liraglutide randomized controlled trials provide strong evidence of a causal association between liraglutide exposure and pancreatic cancer." (Doc. No. 3586-10 at 58.) Defendants argue that Dr. Madigan's opinions should be excluded because the methodology employed in his meta-analysis was marred by the biased selection of pancreatic cancer event counts. The Court agrees.

As a primary example, Dr. Madigan failed to apply consistent criteria for counting pancreatic cancer events in his analysis. According to Dr. Madigan's deposition testimony, he counted only "events that were adjudicated as pancreatic cancer by the neoplasm EAC [12] ." (Doc. No. 3586-4 at 25–27). While Dr. Madigan applied this restrictive standard to the placebo group, he did not apply the same stringent standard to the liraglutide group. Dr. Madigan included one non-adjudicated event in the liraglutide group, but did not similarly include several non-adjudicated events in the placebo group. (Doc. No. 3586-4 at 12 (noting the inclusion of an event in liraglutide that was never adjudicated).) As another example, Dr. Madigan included non-pancreatic ductal adenocarcinoma ("PDAC") tumors for liraglutide but excluded a non-PDAC tumor for the placebo group. (Doc. No. 3586-4 at 67–68.)

12 EAC is an abbreviation for event adjudication committee.

Consequently, Dr. Madigan's selective approach resulted in an inflated count of liraglutide events and a deflated count of placebo events. The Court therefore finds that Dr. Madigan's unequal application of criteria among the two groups inevitably skews the data and critically undermines the reliability of his analysis. *See* *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig. (No. II) MDL 2502*, 892 F.3d 624, 634 (4th Cir. 2018) ("Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion.").

Further casting doubt on the reliability of his methodology, Dr. Madigan's decision to count only cases adjudicated by the neoplasm EAC is different from the method he employed in 2015. In his initial meta-analysis in 2015, Dr. Madigan cited non-adjudicated sources to identify pancreatic cancer event counts. (Doc. No. 3586-10 at 27.) He also testified in 2015 that an adjudication does "[n]ot necessarily" improve the reliability of a study, and explained that the value of using the adjudication counts "depends on how the adjudication is performed." (Doc. No. 3586-3 at 51.) Shifting gears and failing to heed his earlier standard of proper methodology, however, Dr. Madigan restricted his 2019 meta-analysis to only events adjudicated by the neoplasm EAC without considering how the adjudication was performed in the studies. (Doc. No. 3586-4 at 23.) The Court finds that Dr. Madigan's subsequent change in chosen methodology, without explanation or mention of it in his updated report, suggests a lack of scientific rigor. *See, e.g.*, *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) (noting than an expert's violation of his own standard of proper methodology "suggests that he does not apply the same rigor in the courtroom that he would apply to his [scientific] endeavors").

Additionally, the Court notes that Dr. Madigan's analysis was limited to a small universe of data provided to him. (Doc. No. 3586-4 at 4.) He did not conduct a comprehensive search of the published peer-reviewed literature for studies evaluating whether incretin-based drugs are associated with an increased risk of pancreatic cancer, and thereby disregarded independent research at odds with his testimony. (*Id.* at 8–9.) Dr. Madigan offered no meaningful explanation as to why he did not search for or consider these studies other than to say, "It was not what I was asked to do." (*Id.* at 9.) This testimony, coupled with the aforementioned biased selection of data, gives the Court great pause. *See McEwen v. Balt. Wash. Med. Ctr. Inc.*, 404 F. App'x 789, 791 (4th Cir. 2010) (indicating that an expert's "fail[ure] to meaningfully account for medical literature at odds with their testimony" is a basis for a finding on unreliability). *See also* *Daubert II*, 43 F.3d

at 1317 ("One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying.").

***21** Moreover, Dr. Madigan's constrained approach clearly contradicts his testimony in 2015 that the scientifically appropriate methodology to determine causal association is to "consider multiple threads of evidence; such as animal studies, potentially spontaneous reports in this context, observational studies of various kinds, clinical trials, if they are available." (Doc. No. 3586-3 at 25.) Again, he did not do this here. As such, the Court finds that Dr. Madigan's analysis does not fall "within the range of accepted standards governing how scientists conduct their research and reach their conclusions."[13] *Daubert II*, 43 F.3d at 1317. For the foregoing reasons, the Court finds that Dr. Madigan has not employed "good science" and therefore excludes his testimony. *See* *Daubert I*, 509 U.S. at 593, 113 S.Ct. 2786

13 Plaintiffs' attempt to save Dr. Madigan's opinions by asserting that it is consistent with Cao's 2019 meta-analysis is unavailing. In particular, Plaintiffs claim that Dr. Madigan's finding of a 2.46 odds ratio associated with liraglutide corresponds with the 2.91 odds ratio derived from the Cao publication. However, the purported 2.91 odds ratio appears nowhere in the publication and is directly at odds with the study authors' finding of no increased risk of pancreatic cancer associated with GLP-1RAs, including liraglutide. (Doc. No. 3586-7 at 309, 311, 313.) Plaintiffs' counsel's own analysis of the data in the Cao publication cannot substitute for reliable expert opinion. *See* *Barcamerica Int'l USA Tr. v. Tyfield Imps., Inc.*, 289 F.3d 589, 593 n.4 (9th Cir. 2002) (noting that "the arguments and statements of counsel 'are not evidence and do not create issues of material fact' ") (citation omitted).

b. Dr. Wells

Dr. Wells is Plaintiffs' other biostatistics expert; he offers the opinion that there is "strong evidence of a causal association between GLP-1 exposure and pancreatic cancer." (Doc. No. 3586-5 at 3.) Dr. Wells does not offer an opinion as to sitagliptin or other DPP-4 inhibitors. (*Id.* at 40.) Defendants argue that Dr. Wells' testimony should be excluded because his methodology has been unreliably applied due to his "cherry-picking of studies and selection of pancreatic cancer cases." (Doc. No. 3586-1 at 41.) The Court agrees.

Beginning with exenatide, Dr. Wells testified that when he included the EXSCEL study in his meta-analysis along with the other exenatide clinical trials, the results were "consistent with no risk." (Doc. No. 3586-5 at 86.) And only when he excluded EXSCEL did he get a result of an increased risk for exenatide. (*Id.* at 86–87.) While Dr. Wells explained in his report that he excluded EXSCEL because "there was a high pancreatic cancer event rate in the comparison group as compared to background rate in the general population," (*id.* at 11.), he later admitted in his deposition that the background rate in EXSCEL's comparison group "is not higher" than the expected rate he cited in his report, (*id.* at 79). Dr. Wells attempted to adjust his explanation by testifying that he excluded EXSCEL because the incident rates in the comparator arm was twice that in LEADER, the liraglutide clinical study. (*Id.* at 72–73.) Dr. Wells offered no reason as to why it would be scientifically sound to base the exclusion of the EXSCEL study based on a comparison to LEADER's background rate. Without sufficient indicia of reliability, the Court declines to find that his exclusion of EXSCEL was scientifically sound. *See generally* *Metabolife Int'l, Inc. v. Wornick*, 264 F.3d 832, 840–41 (9th Cir. 2001) ("[T]he district court acts as a 'gatekeeper,' excluding 'bad science' that does not carry sufficient indicia of reliability for admission under Rule 702.").

Further undercutting the reliability of his analysis, if Dr. Wells had applied the same standard for exclusion as that stated in his report for excluding EXSCEL—namely, that the number of incidents in the study's comparator group was outside the expected background rate—Dr. Wells would have also excluded LEADER from his analysis because, as stated in his deposition, the incident rate in LEADER's placebo arm was below the expected background rate. (Doc. No. 3586-5 at 83.) Dr. Wells, however, did not similarly exclude LEADER, and therefore did not apply his apparent standard evenly. There being no adequate scientific reason to exclude EXSCEL—a large-scale clinical trial accounting for ninety percent of relevant exenatide data—from his analysis, the Court finds Dr. Wells' exclusion of the EXSCEL study arbitrary and therefore not properly grounded in science. *In re Bextra & Celebrex Mktg. Sales Practices & Prod.*

Liab. Litig., 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (finding that an expert who reaches his opinion by "cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion" is not admissible because the "opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not "good science"); *See* *In re Lipitor II*, 892 F.3d at 634 ("Courts have consistently excluded expert testimony that 'cherry-picks' relevant data.") (alteration and citation omitted).

***22** Turning to liraglutide, Dr. Wells stated that he excluded three liraglutide clinical trial studies from his analysis because the patients in those studies were also taking insulin. He explained that excluding those trials ensured "intervention fidelity," which means that he did not want the possibility of insulin interacting with liraglutide in a manner that would affect his analysis. (Doc. No. 3586-5 at 120–21.) Dr. Wells, however, did not apply this criterion consistently because he included LEADER—a study in which more than half of the patients took insulin—in his analysis. (*Id.* at 121, 125.) While Dr. Wells admitted that he was not aware that a number of patients in LEADER also took insulin, he has not updated his report to account for his critical oversight. Dr. Wells' inconsistent application of the "intervention fidelity" principle resulted in the exclusion of three trials—all of which reported fewer pancreatic cancer events in liraglutide than in the placebo arm. This inevitably prejudiced Dr. Wells' analysis and signals to the Court that he did not conduct his analysis reliably or with scientific rigor.

Additionally, similar to Dr. Madigan, Dr. Wells failed to apply a consistent standard for inclusion and exclusion of pancreatic cancer events in his liraglutide analysis. Like Dr. Madigan, Dr. Wells counted both PDAC and non-PDAC events for liraglutide, but counted only PDAC events for the placebo group. (*Id.* at 8, 89–91; Doc. No. 3827-2 at 82–83.) Dr. Wells also stated that in counting pancreatic cancer events, he was "using the numbers that were adjudicated" (Doc. No. 3586-5 at 93), but when asked why he excluded four placebo events adjudicated by the death adjudication committee, Dr. Wells offered no meaningful explanation other than "I was just using the information from the main results table ... I wasn't using death adjudication" (*id.* at 114). Further applying his stated method of counting adjudicated cases in an unreliable manner, Dr. Wells counted a non-adjudicated event for liraglutide in his analysis. (*Id.* at 8.) As previously discussed, the Court declines to find that such disparate treatment between the liraglutide and placebo counts amounts to "good science." *See* *Daubert I*, 509 U.S. at 593, 113 S.Ct. 2786; *In re Lipitor II*, 892 F.3d at 634 ("cherry-picking[ ] undermines principles of the scientific method").

Moreover, the Court finds that Dr. Wells' methodology of combining exenatide and liraglutide data, which resulted in his conclusion that "there is strong evidence of a causal association between GLP-1 exposure and pancreatic cancer," is unreliable because he did not consider relevant clinical trial data from other GLP-1 RAs. Granted, Dr. Wells explained that he grouped only exenatide and liraglutide together because they "have different pharmacokinetic properties ... there's different doses, different -- the mechanism of action. There's different half-lives, different methods of injection or pill or methods of delivery" compared to other GLP-1 receptor agonists. (Doc. No. 3586-5 at 60–61.) Critically, however, he admitted that he is not qualified to opine on the differences between GLP-1 RAs and did not know whether differences between liraglutide and exenatide were more or less than any other GLP-1 RA. (*Id.* at 61.) And ultimately, Dr. Wells testified that the decision to limit his analysis to exenatide and liraglutide clinical trials, to the exclusion of other GLP-1 RAs' trials, was not his own, but of Plaintiffs' counsel. (*Id.*)

The record also shows that each of the peer-reviewed and published GLP-1 RA meta-analyses combines all of the relevant clinical trial data. (Doc. No. 3586-1 at 77–78.) None of have employed Dr. Wells' approach, and none report that GLP1-RAs cause an increased risk of pancreatic cancer. These circumstances support a finding that Dr. Wells "developed [his] opinions expressly for purposes of testifying," and that his analysis was unduly results-driven. *Daubert II*, 43 F.3d at 1317, 1319 (noting that if an expert's testimony does not stem from research independent of litigation, the expert must point to some objective source "to show that they have followed the scientific method, as it is practiced by (at least) a recognized minority of scientists in their field"); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d 781, 797 (N.D. Cal. 2020) (excluding an expert's "unduly results-driven" analysis).

***23** For the foregoing reasons, the Court finds that Dr. Wells' analysis consists of a cherry-picked selection of favorable data. Consequently, it is unduly results-driven, not good science, and therefore inadmissible. *See* *Lust*, 89 F.3d at 596 (affirming the district court's finding that an expert may not "pick and [choose] from the scientific landscape and

present the Court with what he believes the final picture looks like."); *Domingo ex rel. Domingo v. T.K.*, 289 F.3d 600, 605 (9th Cir. 2002) ("Scientific evidence is deemed reliable if the principles and methodology used by the expert proffering it are grounded in the methods of science."). Accordingly, the Court excludes Dr. Wells' testimony.

c. Dr. Brown

Dr. Brown is Plaintiffs' biological plausibility expert, who theorizes that incretin-based therapies promote the development of pancreatic cancer because they activate GLP-1 signaling in certain pancreatic cells, causing those cells to proliferate, which in turn, causes cancer. (Doc. No. 3586-15 at 40.) Dr. Brown's theory, however, is not supported with sufficient evidence to meet the standard of reliability under Rule 702.

As an initial matter, the Court notes that Dr. Brown's hypothesis has not been tested in humans, and finds this deficiency significant in light of several clinical trials and meta-analyses concerning the pancreatic safety of incretin-based therapies which report no statistically significant increased incidence of pancreatic cancer associated with incretin mimetics. *See In re Denture Cream Products Liab. Litig.*, 795 F. Supp. 2d 1345, 1367 (S.D. Fla. 2011) ("Hypotheses are verified by testing, not by submitting them to lay juries for a vote."). The Court also notes that "[a]nimal studies are not generally admissible where contrary epidemiological evidence in humans exists." *In re Silicone Gel Breast Implants Prod. Liab. Litig.*, 318 F. Supp. 2d 879, 891 (C.D. Cal. 2004). And this is not a case where contrary epidemiological evidence is scarce or lacking.

Moreover, while "animal studies can be used to support theories on human health, [ ] the district court retains its gatekeeper function in requiring analytical support for the extrapolation from animals to humans." *Domingo*, 289 F.3d at 606. In his deposition, Dr. Brown testified that there are fundamental biological differences between animals and humans, including that mice have two insulin genes while humans have only one, and that mice and rats are more susceptible to developing cancer than human beings. (Doc. No. 3586-5 at 158–60.) Despite these differences, however, Dr. Brown's hypothesis has not been tested in humans. (*Id.* at 152.)

Plaintiffs assert that the *in vitro* human tissue data[14] that Dr. Brown reviewed are sufficient to validate his hypothesis, but "[i]t is not always clear that one can generalize findings from the artificial setting of tissues in laboratories to whole human beings." *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005) (citation and internal quotations omitted). "[E]xtrapolation from animal studies to humans cannot be done uncritically." *Id.* Significant here, Dr. Brown did not evaluate whether the dose used in the animal studies upon which he relied, were similar to those administered to humans. (Doc. No. 3586-5 at 442–43.) According to Dr. Brown: "I just didn't have time ... so I don't know if it was comparable or not." (*Id.* at 443.) In its gatekeeping role, the Court's objective "is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co.*, 526 U.S. at 152, 119 S.Ct. 1167. The difference in animal and human dosages is an important consideration for purposes of a reliable extrapolation. *See, e.g.*, *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d at 407 (noting that "the high doses often used in animal studies may not correspond to considerably lower concentrations of a drug or other substance to which humans are in reality exposed"). As such, Dr. Brown's failure to compare the animal and human dosages because he "just didn't have time" shows the Court that he did not employ the same level of intellectual rigor expected of an expert in his field. *See* *Kumho Tire Co.*, 526 U.S. at 152, 119 S.Ct. 1167. Thus, the Court finds that Dr. Brown conducted an unreliable extrapolation, which in turn, undermines the scientific validity of his theory.

14 "[R]esearchers frequently conduct experiments on cell and tissue cultures. These experiments, sometimes referred to as in vitro studies to distinguish them from studies performed in vivo, meaning on live humans and animals, also are subject to the problem of extrapolation." *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d at 407.

***24** Moreover, similar to the previously discussed experts, Dr. Brown limited his ability to reliably opine and account for data at odds with his opinion because he did not review a large body of relevant animal data—including life-long carcinogenicity studies conducted with all of the medications in this litigation, Defendants' post-approval

studies conducted in diabetic animals, and the over 250 toxicological studies evaluating the safety of incretin-based therapies. (Doc. No. 3586-5 at 164–65, 166, 421–22.) Dr. Brown's selective review of data—which is wholly contrary to his stated methodology that the totality of evidence must be considered to avoid bias and reliability issues—only further casts doubt on the reliability of the methods he employed in this case. (*Id.* at 418 (Dr. Brown testifying, "if the totality and objectiveness are not considered, there is likelihood of bias and, in fact, may be unreliable").)

Further, as the Ninth Circuit noted in *Domingo ex rel. Domingo v. T.K.*, a mechanism expert must support "every necessary link" in their biological theory with supporting evidence. 289 F.3d at 606–07. In his deposition, Dr. Brown confirmed that his ultimate opinion is that based on animal and other preclinical data, it is biologically plausible that incretin mimetics "can contribute to and promote the progression of pancreatic cancer in predisposed individuals." (Doc. No. 3586-5 at 148.) However, other than a KRAS mutation, Dr. Brown could not define how a "predisposed individual" could be identified in the real world, and could not quantify to what extent incretin-based therapies increase the risk of pancreatic cancer in humans. (*Id.* at 148–50.) Moreover, Dr. Brown affirmed that he was not aware of any animal studies in which the animals treated with incretin-based drugs actually developed pancreatic cancer. (*Id.* at 161.) These unfilled gaps leave much room for speculation and do little to earn the Court's confidence that Dr. Brown's theory has sufficient scientific support.

Dr. Brown also acknowledged that if GLP-1 signaling was, as he hypothesized, promoting the development of pancreatic cancer, there would need to be evidence of either overexpression of the GLP-1 gene coding or an increase in the affinity of GLP-1 receptors in pancreatic cancer cells and precursors. (*Id.* at 188–89.) However, Dr. Brown admitted that the literature has not reported overexpression and that he has not studied whether there is an increased affinity for the receptors. (*Id.* at 188–90.) As such, by Dr. Brown's own testimony, there is insufficient evidence to support the last link of his theory: GLP-1 signaling to carcinogenesis. [15] Without more, Dr. Brown's theory does not pass reliability standards. *See* *Domingo*, 289 F.3d at 606–07 (noting that each link of the hypothesis must be "based on objective, verifiable evidence and scientific methodology of the kind traditionally used by experts in the field.").

15 Plaintiffs' argument that overexpression or increased affinity is irrelevant to Dr. Brown's opinion is belied by his deposition testimony. Moreover, Plaintiffs' citation in their opposition brief to studies that purportedly show increased affinity in receptors from "the same family" as GLP-1 receptors is unavailing. (Doc. No. 3727 at 71.) Dr. Brown did not testify about these studies, and they are not included in his report. The Court further notes that as a biological plausibility expert who is not offering a medical causation opinion, Dr. Brown's testimony, alone, is insufficient to prove general causation. *See generally In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d at 791 (noting that biological plausibility "is only a subsidiary consideration in the larger question of general causation").

Considering these aforementioned gaps, the Court finds Dr. Brown's hypothesis more speculative than helpful to a jury. As the court in *In re Denture Cream Prod. Liab. Litig.* noted:

> ***25** Plaintiffs' experts have based their conclusions on a modest amount of animal studies, mechanistic processes, epidemiological studies, and case studies ... [The] theory is not ridiculous, but neither is it necessarily true; it is ripe for testing. In short, taking everything together, there is enough data in the scientific literature to hypothesize causation, but not to infer it. Hypotheses are verified by testing, not by submitting them to lay juries for a vote.

795 F. Supp. 2d at 1367. For the foregoing reasons, the Court concludes that Dr. Brown's hypothesis is not supported by sufficiently reliable principles and evidence to raise it above inadmissible speculation, and thus, excludes his testimony. *See* *Joiner*, 522 U.S. at 146, 118 S.Ct. 512 ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."); *Domingo*, 289 F.3d at 606–07; *see also* *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 677 (6th Cir. 2010) ("[W]hat science treats as a

useful but untested hypothesis the law should generally treat as inadmissible speculation.").

d. Dr. Gale

Dr. Gale is Plaintiffs' sole medical causation expert; he opines that based on his application of the "weight of the evidence" methodology, "it is more likely than not exposure of persons with diabetes to GLP-1 agonists and/or DPP-4 inhibitors causes and/or contributes to the development of pancreas cancer in humans." (Doc. No. 3586-15 at 285.) Defendants assert that Dr. Gale's testimony should be excluded because he did not weigh all of the evidence, and that his opinion about the latency of pancreatic cancer relies on evidence that does not concern incretins. The Court agrees.

According to Dr. Gale's reports and deposition testimony, he applied the "weight-of-the-evidence approach." (Doc. Nos. 3586-5 at 325–26; 3586-15 at 226–27.) As indicated in his report, this approach "emphasize[s] the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents." (Doc. No. 3586-15 at 227.) Dr. Gale further noted that "[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to **all relevant information**." (*Id.* (emphasis added by Dr. Gale).) And as Plaintiffs point out, "it is not intrinsically unscientific for experienced professionals to arrive at a conclusion by weighing all available scientific evidence." (Doc. No. 3727 at 78.) That is not, however, what Dr. Gale did here.

Critically, when Dr. Gale updated his report in 2019, he failed to independently analyze relevant epidemiological data available since 2015 that have not reported a causal relationship between GLP1-RAs or DPP4-Is and pancreatic cancer. These include sitagliptin clinical trial data, LEADER clinical trial data and the FDA's oncology review of the pancreatic cancer events in that study, EXSCEL clinical trial data, and various meta-analyses and observational studies. Dr. Gale's deposition testimony makes this critical shortcoming clear. (Doc. No. 3586-5 at 290 ("Q. [i]f data has come out that's epidemiological in nature related to GLP-1 receptor agonists since your prior reports in 2015, you haven't independently analyzed that data, correct? A. Yes.").) Indeed, Dr. Gale testified that "outside what Dr. Madigan and Dr. Wells have done, [he has not] done any independent epidemiological data analysis" for his 2019 report. (*Id.* at 289). This demonstrates that Dr. Gale failed to reliably apply his stated methodology of considering and weighting all relevant information. (Doc. No. 3586-15 at 227.)

***26** Moreover, Dr. Madigan and Dr. Wells are statisticians, neither of whom can offer a medical opinion in this case. (Doc. Nos. 3586-4 at 61–62; 3586-5 at 33.) Dr. Gale therefore cannot blindly rely on the statistician's reports in forming his medical causation opinion. Rather, prior to relying on other's opinions, he must have first "conducted an independent evaluation of that evidence." *In re Conagra Foods, Inc.*, 302 F.R.D. 537, 556 (C.D. Cal. 2014). Dr. Gale did not do so. As the record shows, Dr. Gale did not independently evaluate the statisticians' reports. For instance, Dr. Gale could not answer simple questions about the scope of the statisticians' meta-analyses, such as the simple question of whether they concerned sitagliptin. (Doc. No. 3586-5 at 288–90.) And Dr. Madigan and Dr. Wells testified that they had not consulted with pancreatic cancer experts, like Dr. Gale, about their 2019 reports. (*Id.* at 34–35; Doc. No. 3827-2 at 44–46.)

Furthermore, Dr. Gale's failure to independently review the statisticians' reports is significant because, as described earlier, Dr. Madigan's and Dr. Wells' reports were marred by a selective review of data and inconsistent application of inclusion criteria. *See supra* § IV.B.1.i.a, b. The Court agrees with Defendants that at a minimum, Dr. Gale needed to, just as the FDA did in reviewing the LEADER data, review the statisticians' reports to determine whether the events included in their meta-analyses were in fact pancreatic cancers and whether those events could have been caused by exposure to the medication—especially given that the statisticians counted a benign tumor and events reported prior to the patient taking medication as pancreatic cancer events. His lack of scientific rigor in this regard is telling. *See* *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d at 563 (a district court in an analogous case finding, "Dr. Gale's selectivity in defining the universe of relevant evidence thus violated his own standard of proper methodology that 'all evidence should be taken into account,' which suggests that he does not apply the same rigor in the courtroom that he would apply to his medical endeavors.") (alteration omitted).

Also cutting against the reliability of Dr. Gale's application of the "weigh-of-the-evidence" methodology, it is unclear from his report and deposition how he weighed the evidence he considered, what weight he gave to them, why he gave them that weight, and how he balanced the weight of certain evidence against others evidence. Courts

have recognized that it is imperative that experts who apply multi-criteria methodologies such as "weight of the evidence" must "rigorously explain how they have weighted the criteria. Otherwise, such methodologies are virtually standardless and their applications to a particular problem can prove unacceptably manipulable. Rather than advancing the search for truth, these flexible methodologies may serve as vehicles to support a desired conclusion." *In re Mirena Ius Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 247 (S.D.N.Y. 2018).

Dr. Gale provided no such rigorous explanation, and without more, his analysis cannot be verified or replicated. Indeed, Dr. Gale testified in 2015 that in order to replicate his conclusion one must "reproduce it in another human being who was a clone of me, then ... expose them to those data and ask them to comment whether it is more likely than not that exposure to incretins causes or it capable of contributing to development of pancreas cancer." (Doc. No. 3586-5 at 328–29). While this statement may have been made out of frustration stemming from a long day of being deposed, the record contains no amended statement or other information to explain what criteria Dr. Gale applied in weighting the evidence such that others may be able to test and replicate his analysis. The Court finds that this deficiency supports exclusion. *See, e.g.*, *Jones v. Novartis Pharms. Corp.*, 235 F. Supp. 3d 1244, 1273 (N.D. Ala. 2017) (finding as unreliable and excluding an expert's weight-of-the-evidence opinion because he did "not describe[ ] the process he used or the steps he took in applying this methodology, including whether he ranked plausible rival explanations"); *In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787, 796 (3d Cir. 2017) (stating that "[t]o ensure that the Bradford Hill/weight of the evidence criteria is truly a methodology, rather than a mere conclusion-oriented selection process there must be a scientific method of weighting that is used and explained" and "all of the relevant evidence must be gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science.") (alterations and citations omitted).

***27** In addition to the above, other record evidence reveals that Dr. Gale has not employed the same level of intellectual rigor in developing his opinions in this litigation as he would in the scientific community as a pancreatic cancer expert. *See* *Kumho Tire Co., Ltd.*, 526 U.S. at 152, 119 S.Ct. 1167 (a trial judge must "make certain that an expert ... employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field"). Notably, in 2016, Dr. Gale published an article titled *Recent Progress and Concepts in Pancreatic Cancer*, in which he "consider[ed] several areas of recent interest, progress, and controversies including pancreatic cancer biology, mutational landscape, the concept of latency, and *causes of pancreatic cancer*." (Doc. No. 3586-16 at 2 (emphasis added).) Despite concluding in his 2015 expert report that it is more likely than not that GLP-1RAs and DPP-4Is cause or contribute to the development of pancreatic cancer, the 2016 article makes no mention of incretin-based therapies. (*Id.* at 7–9.) Tellingly, although the article delineated a breadth of pancreatic cancer risk factors, ranging from those most strongly associated with pancreatic cancer (cigarette smoking) to those less convincingly associated with pancreatic cancer (coffee consumption), Dr. Gale chose not to include in this article the conclusion that he espouses here —that is, that incretin-based drugs more likely than not cause pancreatic cancer. (*Id.* at 8.)

Given the discrepancy between what Dr. Gale endorses in this litigation and in the scientific community, the Court finds that Dr. Gale has not approached his opinions in this case with "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co., Ltd.*, 526 U.S. at 152, 119 S.Ct. 1167. *See also* *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1236 (9th Cir. 2017) ("unwillingness to publish weighs against admissibility"). Also telling is that despite years of research into the pancreatic safety of incretin mimetics conducted by various medical, scientific, and regulatory entities, Dr. Gale is alone in concluding that GLP-1RAs and DPP-4Is cause or contribute to pancreatic cancer development. These circumstances do not signal a faithful application of an accepted methodology. *See* *Lust*, 89 F.3d at 598 ("When a scientist claims to rely on a method practiced by most scientists, yet presents conclusions that are shared by no other scientist, the district court should be wary that the method has not been faithfully applied."). Thus, for the foregoing reasons, the Court finds that Dr. Gale's causation opinion is inadmissible, and consequently, must be excluded. *See* *id.*; *Kumho Tire Co., Ltd.*, 526 U.S. at 152, 119 S.Ct. 1167; *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d at 798–89 (finding that the expert "opinions must be excluded" because "despite substantial research on the issue over many years, plaintiffs' experts apparently stand alone" and "there simply is no interpretation by anyone other than plaintiffs' experts that supports general causation").

Dr. Gale also offered an opinion concerning latency. Specifically, he opines that "development of pancreases [sic] cancer within 1-2 years of exposure to incretions is entirely compatible with incretin exposure being a cause or a substantial contributing factor to someone developing pancreas cancer." (Doc. No. 3586-15 at 282.) The Court agrees with Defendants that his latency opinion lacks foundation because the literature from which he extrapolates his conclusion does not concern incretins, and he has not explained why such an extrapolation is scientifically sound. As such, other than his say so, Dr. Gale has not pointed to relevant evidence to support his conclusion that incretin-based therapies can cause pancreatic cancer to develop in as little as one-to-two years. *See* *Joiner*, 522 U.S. at 146, 118 S.Ct. 512 ("Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."); *Stephens v. Union Pac. R.R. Co.*, 935 F.3d 852, 856 (9th Cir. 2019) (an "expert's opinion must rest on facts or data in the case that the expert has been made aware of or personally observed, not merely assumptions and speculation."). Thus, the Court also finds Dr. Gale's latency opinion inadmissible.

***28** Accordingly, based on the foregoing, the Court will grant Defendants' motion to exclude the opinions of Drs. Madigan, Wells, Brown, and Gale.

ii. Motion to Exclude Drs. Landolph, Woolf, and Taylor

Defendants also jointly move to exclude the opinions of Plaintiffs' experts, Drs. Landolph, Woolf, and Taylor. [16] (Doc. No. 3521.) Dr. Landolph is a chemical toxicologist, who evaluated whether there is a viable mechanism whereby incretin-based therapies could contribute to the development of pancreatic cancer. (Doc. No. 3728 at 12.) Dr. Woolf is a gastroentologist, who performed a literature review to assess whether incretin mimetics more likely than not increase the risk of pancreatic cancer. (*Id.* at 21–22.) Dr. Taylor is a pathologist, who examined non-human primate slides from two toxicology studies involving exenatide. (*Id.* at 28–29.) The Court discusses the merits of Defendants' motion to exclude these experts in turn.

16 Initially, Defendants also moved to exclude the expert opinion of Dr. Betensky, but Plaintiffs have since withdrawn her as an expert in this litigation, and Defendants have correspondingly withdrawn their motion to exclude Dr. Betensky. (Doc. Nos. 3702, 3703.) The Court therefore considers only the remaining experts subject to the instant motion. (Doc. No. 3521.)

a. Dr. Landolph

Dr. Landolph is a chemical toxicologist and carcinogenesis consultant, who submitted a report in 2015, offering the opinion that after weighing all of the evidence, incretin-based therapies are capable of contributing to the development of pancreatic cancer. (Doc. No. 3728-2 at 61.) However, because Dr. Landolph conducted an incomplete review of the relevant evidence and failed to update his 2015 report, the Court finds his opinion inadmissible.

According to Dr. Landolph, to determine whether an agent is carcinogenic, the totality of evidence must be reviewed. (Doc. No. 3521-2 at 61–62 ("what we do is integrate the totality of evidence to come to a decision as to whether this compound is a carcinogen, or not.").) He also explained that conducting "good science" requires looking at "clinical trials, epidemiology data ... all the data you can get." (Doc. No. 3826-5 at 5.) Dr. Landolph, however, did not do that here. As evidenced by his deposition testimony, Dr. Landolph failed to consider all available clinical trial data, observational studies, and other epidemiological literature on incretin-based therapies. (*See, e.g.*, Doc. No. 3521-2 at 74, 85–86, 95.) Tellingly, Dr. Landolph repeatedly testified in 2015 that he wished to supplement his report to include new literature on pancreatic cancer. (*Id.* at 54.) New literature, large-scale clinical trials, and meta-analyses concerning the relationship between incretin-based therapies and pancreatic cancer have been published and made available since 2015. Yet, despite having over five years to submit a supplemental report accounting for this data—which in his own words is highly relevant to forming an opinion on a substance's carcinogenicity—Dr. Landolph submitted none. [17]

17 This Court's decision to excuse the expert's failure to consider evidence in *Johns v. Bayer Corp.* does not excuse Dr. Landolph's failure to review the relevant data here. Unlike Dr. Landolph, the expert in *Johns* was not offering a causation opinion

> or employing a methodology based on weighing all the relevant evidence. The Court reiterates that Dr. Landolph's conclusions are premised on weighing all the relevant evidence, and in 2015, he testified that "good science" requires reviewing all available clinical and epidemiological data, and that he wished to supplement his report with additional data. Furthermore, unlike in *Johns*, the Court is evaluating the reliability, as opposed to relevance, of Dr. Landolph's expert opinion. As such, *Johns* does not support admission of Dr. Landolph's opinions.

***29** And while the Court acknowledges that Dr. Landolph testified that he "put more of [his] effort into the preclinical studies and the animal carcinogenesis studies, genotoxicity, et cetera," (*id.* at 95), Dr. Landolph also admitted that he did not review various relevant animal studies—including carcinogenicity studies in rodents from the manufacturers of incretin-based therapies and peer-reviewed published articles reflecting studies performed using incretin-based therapies in animal models with Type II diabetes, (*id.* at 103–104). The incompleteness of Dr. Landolph's review reveals that he failed to faithfully apply his own standard for "good science." Consequently, the Court finds that his 2015 report is not founded on reliable scientific reasoning. *See* *Kennedy,* 161 F.3d at 1230 ("The *Daubert* duty is to judge the reasoning used in forming an expert conclusion. The test is whether or not the reasoning is scientific and will assist the jury."); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d at 798 ("The amendment [to Rule 702] specifically provides that the trial court must scrutinize not only the principles and methods used by the expert, *but also whether those principles and methods have been properly applied to the facts of the case.*") (quoting Fed. R. Evid. 702 advisory committee's note) (emphasis added); *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d at 563 (noting that an expert's deviation from his standard of proper methodology is indicative of a lack of scientific rigor).

Lastly, the Court declines to accept Plaintiffs' invitation to interpret the Ninth Circuits' decisions in *Wendell* and *Kennedy* as permission to excuse an expert's failure to consider relevant animal and epidemiological studies where it exists. Each case is distinguishable. *Wendell* involved "an exceedingly rare cancer" for which animal and epidemiological studies were unavailable because the scientific community had "not invested substantial time or resources into investigating the causes of such a rare disease." 858 F.3d at 1236. Similarly, in *Kennedy*, the expert explained that epidemiological studies linking the substance and injury at issue "would be almost impossible to perform." 161 F.3d at 1228. As such, the district court erred in excluding the expert based on the lack of specific studies proving general causation and the medical community's absence of consensus on that point. *Id.* at 1228–29. Here, as previously discussed, the medical, scientific, and regulatory communities have devoted substantial time and resources investigating the pancreatic safety of incretin-based therapies. The absence or impracticality of obtaining animal and epidemiological evidence in *Wendell* and *Kennedy* are simply not present here. [18] Accordingly, for the foregoing reasons, the Court excludes Dr. Landolph's opinions.

18 The Court also finds Plaintiffs' reliance on *In re Berg Litig.* unavailing. That case involved a substance "that is known to be capable of causing harm" and for which "there is no threshold harmful dosage level." 293 F.3d 1127, 1129 (9th Cir. 2002). Noting that the substance can cause harm at any level, the Ninth Circuit found that the district court's adoption of a "doubling of the risk" standard, at the general causation phase, was error. *Id.* at 1129–30. Here, Defendants' drugs are not known or generally accepted as capable of causing pancreatic cancer. Thus, *In re Berg Litig.* is distinguishable.

b. Dr. Woolf

Dr. Woolf is a gastroentologist, who based on his literature review concluded that it is more likely than not that incretin-based therapies are causally associated with an increased incidence of pancreatic cancer. (Doc. No. 3728-2 at 157–58.) According to Dr. Woolf, the focus of his opinions in this case was on the pathway that shows a relationship between incretin mimetics and pancreatic cancer, a process in which PanIN lesions play a well-defined role. (Doc. Nos. 3521-2 at 115–16; 3728-2 at 152.) However, apart from the "on-the-job" training he received in this litigation, Dr. Woolf has conducted no research on, or had any experience with, PanINs. (Doc. No. 3521-2 at 116.) Indeed, Dr. Woolf admitted that it was

Plaintiffs' counsel who first taught him about the alleged relationship between incretins and pancreatic cancer:

> ***30** Q: What did [Plaintiffs' counsel, Brian DePew] teach you in this litigation?
>
> A: Well, he taught me all the information on pancreatitis ... as well as relationships between PanINs and the incretins.
>
> Q: So your formal education on the topic of the relationship between incretins and pancreatitis started with Mr. DePew?
>
> A: Started with him, exactly.
>
> Q: And your learnings concerning the alleged relationship between incretins and pancreatic cancer started with Mr. DePew?
>
> A: Correct.

(*Id.* at 118.) That the sum of Dr. Woolf's knowledge regarding the specific issues about which he opined was derived solely from his experience in this litigation gives the Court great pause as to the reliability and independence of his report. *See* *Daubert II*, 43 F.3d at 1317 ("[I]n determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.").

Additionally troubling is that Dr. Woolf failed to review relevant clinical trials and conceded that he "should have." (Doc. No. 3826-6 at 4.) Tellingly, despite the benefit of additional years to update his report and review various literature, including many concerning clinical trials, that have been published since 2015, Dr. Woolf did not provide a supplemental report. (*Cf.* Doc. No. 3521-2 at 148 ("You would like to be able to [review all the relevant studies], but there's a time constraint.").) *See also* *Lust*, 89 F.3d at 596 (an expert may not "pick and [choose] from the scientific landscape and present the Court with what he believes the final picture looks like.").

And even in his review of a limited universe of literature in 2015, Dr. Woolf failed to consider the entirety of certain studies, relying only on their abstracts. For example, Dr. Woolf admitted that one of the articles he found to be of interest is Waser's *Glucagon-Like Peptide 1 Receptor Expression in Normal and Diseased Human Thyroid and Pancreas*. (Doc. No. 3521-2 at 133.) According to Dr. Woolf he did not read the full article and relied only on the abstract because he "would have to pay for it." (*Id.*) Other explanations he offered for his limited review of available literature include "it wasn't available on the computer for me" and "there's a time constraint"—reasons which have no scientific basis and only further highlight the unreliability of his opinions. *See* Fed. R. Evid. 702(b)–(c) (an expert's testimony must be "based on sufficient facts or data" and "the product of reliable principles and methods"). Moreover, Dr. Brown's failure to completely read and review the materials he relied upon reveals that he failed to reliably apply his chosen methodology of "review[ing] the paper[s] and look[ing] at the biases, what are the advantages and disadvantages of the study" (Doc. No. 3521-2 at 169). *See* Fed. R. Evid. 702(d) (require the expert to have "reliably applied the [reliable] principles and methods to the facts of the case").

The Court also notes that Dr. Woolf's report concludes that "there is sufficient evidence to causally associate incretin mimetics (including exenatide and DPP-4 inhibitors) with an increased incidence of pancreatic cancer." (Doc. No. 3728-2 at 157–58.) Yet, in his deposition, he could not offer a definition for association and stated that he does not understand there to be a difference between causal association and association. (Doc. No. 3521-2 at 119–20). And despite opining that incretin-based drugs are causally associated with an increased incidence of pancreatic cancer, Dr. Woolf did not attempt to quantify or otherwise meaningfully define the association he observed. (*Id.* at 124.) Without adequate indicia of reliability, the Court declines to find that Dr. Woolf's analysis amounts to "good science." Thus, for the reasons stated, Dr. Woolf's opinions regarding causal association are unreliable. Accordingly, the Court excludes Dr. Woolf's opinions.

c. Dr. Taylor

***31** Dr. Taylor is a pathologist, who opines that based on his examination of slides for exenatide-treated monkeys and baboons from two published studies, "there's a cause for concern" that incretin-based therapies cause pancreatic cancer. (Doc. No. 3521-2 at 184.) While he concedes that he is not offering an ultimate causation opinion, he maintains that "there are some signals out there that indicate that they do increase the risk of cancer." (*Id.*) As an initial matter, the Court notes that aside from this litigation, Dr. Taylor has never

reviewed toxicology slides in monkeys and does not consider himself an expert at reading such slides. (*Id.* at 525–26.)

Importantly, the record demonstrates that Dr. Taylor's methodology of applying the human PanIN classification system to non-human primates is not a reliable scientific method. Dr. Klimstra—one of the developers of the PanIN classification system and the pathologist who coined the term "PanIN"—unequivocally reported that

> the use of the PanIN system in non-human primates to draw any conclusions about the risk to non-human primates to develop pancreatic cancer would be scientifically unreliable. And any conclusion from PanIN-like histology found in non-human primates regarding the assessment of cancer risk in humans would be purely speculative given the current state of science.

(*Id.* at 414.) Plaintiffs do not contest Dr. Klimstra's report.

Furthermore, Dr. Taylor himself admitted that the technique he used has never been used in non-human primates. (*Id.* at 538.) And further casting doubt on the reliability of his methods, Dr. Taylor indicated that he was uncertain over whether applying the human PanIN criteria would be applicable to the non-human primate tissues he was observing, and therefore had to conduct an unblinded review "to see if the criteria applied." (Doc. No. 3521-2 at 533–34.) Lastly, no published literature has applied the human PanIN classification system to non-human primates to assess the risk of cancer. (*See id.* at 537–38.)

Without some objective evidence of the reliability, Dr. Taylor's use of an unvalidated methodology to re-analyze the results of animal studies and reach a conclusion different from the studies' original authors provides grounds for exclusion. *See* *Joiner*, 522 U.S. at 146, 118 S.Ct. 512 ("Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."); *Daubert II*, 43 F.3d at 1316 ("[T]he expert's bald assurance of validity is not enough. Rather, the party presenting the expert must show that the expert's findings are based on sound science, and this will require some objective, independent validation of the expert's methodology."). For the reasons stated, the Court finds that Dr. Taylor's opinions are not supported by sufficient data, and that his method is unreliable. Accordingly, the Court excludes Dr. Taylor's opinions.

Accordingly, based on the foregoing, the Court will grant Defendants' motion to exclude the opinions of Drs. Landolph, Woolf, and Taylor.

iii. Motion to Exclude Drs. Thayer, Wang, and Scharfstein

Having considered Defendants' motions to exclude Plaintiffs' experts, the Court turns to Plaintiffs' motion to exclude Novo's experts, Drs. Thayer, Wang, and Scharfstein. (Doc. No. 3613.) However, the Court need not consider the merits of this motion and denies it as moot, because as more fully explained below, Plaintiffs have not presented evidence to raise a genuine issue of material fact as to general causation. Moreover, the Court does not rely on these experts in granting Defendants' summary judgment motions based on preemption and general causation. [19]

19 As previously noted, while the Court cites in its preemption analysis Dr. Thayer's opinion concerning the reliability of the data in Novo's secondary PDG study, Plaintiffs do not specifically challenge that portion of her report.

2) Causation

***32** Defendants each filed motions for summary judgment based on lack of general causation. (Doc. Nos. 3524, 3525, 3585.) As mentioned earlier, general causation is an essential element in products liability cases. *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d at 1172 (citing *In re Hanford Nuclear Reservation Litig.*, 292 F.3d at 1133); *In re Mirena IUS Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 982 F.3d 113, 124 (2d Cir. 2020) (approving of the district court's "holding that there is a general causation requirement across all states"). Courts define general causation to mean "whether the substance at issue had the capacity to cause the harm alleged." *In re*

Hanford Nuclear Reservation Litigation, 292 F.3d at 1133. In complex pharmaceutical products liability cases, general causation requires expert evidence because the existence of a causal relationship between a substance and the particular harm alleged is outside the common knowledge of lay jurors. *See* *Lust*, 89 F.3d at 598; *In re Nexium Esomeprazole*, 662 Fed App'x 528, 530 (9th Cir. 2016) (affirming summary judgment where the district court excluded plaintiff's expert testimony on general causation); *In re Mirena IUD Prod. Liab. Litig.*, 713 F. App'x 11, 15 (2d Cir. 2017) (approving that "all fifty states typically require expert testimony to prove causation where the causal relationship is outside the common knowledge of lay jurors"). Plaintiffs do not contend otherwise.

As previously analyzed, the opinions of Plaintiffs' experts are unreliable and therefore do not constitute admissible evidence. *See supra* § IV.B.1.i, ii. With no expert evidence to show a causal relationship between incretin-based therapies and pancreatic cancer, Plaintiffs cannot demonstrate a genuine dispute of material fact as to the element of general causation. *See* *Lust*, 89 F.3d at 598. Plaintiffs assert that they can still establish causation through a differential diagnosis because a reliable different diagnosis is sufficient to establish causation.[20] However, the record contains no differential diagnosis evidence, and none of Plaintiffs' experts opined that a differential diagnosis could establish that incretin-based therapies is a cause of pancreatic cancer.

20 "Differential diagnosis is 'the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings.' " *Clausen v. M/V NEW CARISSA*, 339 F.3d 1049, 1057 (9th Cir. 2003) (quoting Stedman's Medical Dictionary 474 (26th ed.1995)).

Moreover, the cases on which Plaintiffs rely for their proposition are distinguishable from this case. Both *Wendell* and *Clausen v. M/V NEW CARISSA* involved cases where the disease at issue occurred so rarely that there is a paucity of literature concerning its causal relationship with the substance at issue. As the Ninth Circuit noted in *Wendell*, "HSTCL[21] is an exceedingly rare cancer, with only 100 to 200 cases reported since it was first recognized. It is not surprising that the scientific community has not invested substantial time or resources into investigating the causes of such a rare disease." 858 F.3d at 1231. And in *Clausen*, the Ninth Circuit opined that "there are good reasons why there is a paucity of literature with respect to the particular scientific theory at issue here—the causal relationship between low level toxic effects of oil and shellfish disease. Oil spills, fortunately, are a rare enough occurrence, and the opportunities for scholarly research are few." 339 F.3d 1049, 1060 (9th Cir. 2003).

21 HSTCL refers to Hepatosplenic T-cell lymphoma.

Unlike HSTCL in *Wendell*, pancreatic cancer is not a rare disease affecting only 100 to 200 individuals since its recognition. *Cf.* 858 F.3d at 1231. Quite opposite, in recent years, pancreatic cancer not only affected, but was estimated to claim the lives of, over 45,000 people. (Doc. No. 3586-5 at 360.) Indeed, Plaintiffs' oncology expert, Dr. Gale, stated himself that pancreatic cancer is "a common form of cancer." (Doc. No. 3828-3 at 4.) Further distinguishing this case from *Wendell* and *Clausen*, the causal relationship between incretin-based therapies and pancreatic cancer has for several years been the topic of various scientific, medical, and regulatory examination, resulting in numerous animal and clinical studies and peer-reviewed literature. The specific issue has been the subject of nine randomized-controlled cardiovascular outcome trials, over two dozen meta-analyses, and hundreds of observational and animal studies. As such, the dearth of studies and literature in *Wendell* and *Clause* are simply not present here. Thus, the Court rejects Plaintiffs' contention that they are entitled to a differential diagnosis to prove general causation in this case. There being no genuine issue of material fact as to the absence of the element of general causation, the Court finds that Defendants are entitled to judgment as a matter of law, and will grant their respective motions for summary judgment on this basis. *See* *Sanchez*, 891 F.2d at 242 (where the moving party presents evidence that no genuine issue of material fact exists, "the nonmoving party has the subsequent burden of presenting significant probative evidence tending to support its claim that material, triable issues of fact remain").

V. CONCLUSION

***33** Accordingly, for the foregoing reasons, the Court:

- **GRANTS** Defendants' joint motion for summary judgment based on preemption (Doc. No. 3594);
- **GRANTS** Defendants' joint motion to exclude Drs. Madigan, Wells, Brown, and Gale (Doc. No. 3586);
- **GRANTS** Defendants' joint motion to exclude Drs. Landolph, Woolf, and Taylor (Doc. No. 3521);
- **DENIES AS MOOT** Plaintiffs' motion to exclude Drs. Thayer, Wang, and Scharfstein (Doc. No. 3613);
- **GRANTS** Defendants' respective motions for summary judgment based on lack of general causation (Doc. Nos. 3524, 3525, 3585).

IT IS SO ORDERED.

All Citations

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